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THERAPY IN CUSHING'S SYNDROME

CUSHING'S SYNDROME INTERPRETED AS HYPERADRENOCORTICISM LEADING TO HYPERGLUCONEOGENESIS: RESULTS OF TREATMENT WITH TESTOSTERONE PROPIONATE[1]

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THIS PRESENTATION will be limited to three lines of thought: (*a*) an enumeration of certain features of Cushing's syndrome, (*b*) an hypothesis concerning the cause of certain of the most important of these and (*c*) the result of therapy based on this hypothesis.

Patients with Cushing's syndrome show at autopsy cancer of one adrenal gland, or a basophil tumor of the pituitary, or neither of these; all cases show the changes described by Crooke (1) in the basophil cells. Although the criteria for the diagnosis of hyperplasia of the adrenal cortex are not altogether established, this condition is undoubtedly present in some of the non-cancer cases, possibly in all (2).

In any case, whether the result of a cancer of the adrenal or otherwise, Cushing's syndrome (3) has an array of clinical features which probably establish it as a disease entity. The primary endocrinopathy in those cases with cancer is almost surely a hyperadrenocorticism. The authors believe that the other cases likewise have hyperadrenocorticism. The evidence is circumstantial. In the first place, cases without adrenal cancer present substantially the same unique clinical picture as those with adrenal cancer. Secondly, hyperplasia of the adrenal cortex has been demonstrated in some of the non-cancer cases which have been carefully studied. This was true in the authors' *case* 3, which likewise had Crooke cell changes and a pituitary adenoma (4). Thirdly, there is certain evidence derived from urinary assays for 17-ketosteroids (5). The excretion of these substances in females is an index (not a measure) of adrenal cortical function. In cases with adrenal cortical cancer the assays are excessively high. In the three female cases without cancer discussed in this paper the values were suggestively high (5). Fourthly, Weil and Brown (6) using a biological test, found an increased excretion of cortin in a case of Cushing's syndrome (*case* 3 of the author's series); similar findings were reported by Anderson, Haymaker and Joseph (7).

The features of Cushing's syndrome which we would emphasize are as follows.

(1) Mild diabetes which is insulin resistant (8).

(2) Muscular weakness, with a low creatinine excretion as an indication of a decreased mass of muscle.

(3) Thin skin, sub-manifestations of which are, *a*), characteristic reddish hue resulting from transparency

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TABLE 1. METABOLIC DATA ON CASE 1

5-Day period	Date	Urine vol.	Dried feces wt.	Pt. wt. 1st Day of period	Calcium				Phosphorus				Nitrogen†		
					Urine	Fecal av. per period	Intake	Balance	Urine	Fecal av. per period	Intake	Balance	Urine	Intake	Balance
	1939	l.	gm.	kg.	gm.	gm.*	gm.	gm.	gm.	gm.*	gm.	gm.	gm.	gm.	gm.
1	3/22–26	7.2	61	53.6	0.45	2.89	3.60	+0.26	0.90	0.85	1.67	−0.08	12.1	23.7	+ 9.2
2	27–31	7.1	58	52.3	0.49	2.89	3.60	+0.22	0.84	0.85	1.67	−0.02	12.9	23.7	+ 8.4
3	4/ 1–5	7.1	72	51.2	0.56	2.89	3.60	+0.15	0.90	0.85	1.67	−0.08	14.6	23.7	+ 6.7
4	6–10	7.3	54	50.4	0.53	3.89	3.60	+0.18	1.07	0.85	1.67	−0.25	17.0	23.7	+ 4.3
5	11–15	7.1	45	49.5	0.43	3.23	3.60	−0.06	1.34	0.95	1.67	−0.62	18.6	23.7	+ 2.7
6§	16–20	5.8	41	48.9	0.47	3.23	3.60	−0.10	1.35	0.95	1.67	−0.63	19.7	23.7	+ 1.6
7	21–25	7.8	27	48.3	0.47	3.23	3.60	−0.10	1.31	0.95	1.67	−0.59	18.8	23.7	+ 2.5
8	26–30	8.9	68	48.4	0.55	3.23	3.60	−0.18	1.26	0.95	1.67	−0.54	20.0	23.7	+ 1.3
9	5/ 1–5	8.2	51	46.9	0.47	2.79	3.60	+0.34	1.30	0.92	1.67	−0.55	19.8	23.7	+ 1.5
10	6–10	8.5	—	46.6	0.55	2.79	3.60	+0.26	1.22	0.92	1.67	−0.47	21.3	23.7	0
11	11–15	8.1	—	46.2	0.49	2.79	3.60	+0.32	1.19	0.92	1.67	−0.44	21.3	23.7	0
12	16–20	8.1	81	45.9	0.57	2.79	3.60	+0.24	1.12	0.92	1.67	−0.37	20.1	23.7	+ 1.2

Studies were interrupted for 30 days because of skin infection in foot, which responded to local treatment. Patient continued to receive α estradiol benzoate in the interim: 1.66 mg. every 3 days for 4 injections after May 20; then 3.32 mg. every 3 days, from June 5 to 20.

13	6/20–24	8.9	44	46.7	0.43	2.69	3.60	+0.48	1.68	0.86	1.67	−0.87	25.5	23.7	− 4.2
14	25–29	9.0	40	45.7	0.40	2.69	3.60	+0.51	1.73	0.86	1.67	−0.92	25.3	23.7	− 4.0

Studies were interrupted for 6 months because of kidney stone. Patient had 2 unreterolithotomies during this time. Patient received α estradiol benzoate from end of period 14 until November 15, 1939; she received 41 injections of 1.66 mg. each.

	1940														
15	1/ 2–6	6.7	85	51.1	0.78	2.92	4.07	+0.37	1.61	0.98	2.61	+0.02	37.6	46.0	+ 3.8
16	7–11	6.8	85	51.1	0.61	2.92	4.07	+0.54	1.78	0.98	2.61	−0.15	37.4	46.0	+ 4.0
17	12–16	7.6	139	51.6	0.55	2.92	4.07	+0.60	1.79	0.98	2.61	−0.16	37.1	46.0	+ 4.3
18	17–21	8.0	84	51.4	0.73	2.92	4.07	+0.42	1.79	0.98	2.61	−0.16	38.1	46.0	+ 3.3
19	22–26	7.4	91	51.1	0.75	2.99	4.07	+0.33	1.49	1.02	2.61	+0.10	34.9	46.0	+ 6.5
20	27–31	6.4	92	51.0	0.75	2.99	4.07	+0.33	1.06	1.02	2.61	+0.53	25.7	46.0	+15.7
21	2/ 1–5	5.7	85	51.7	0.67	2.99	4.07	+0.41	0.78	1.02	2.61	+0.81	21.7	46.0	+19.7
22	6–10	6.2	79	52.4	0.64	3.20	4.07	+0.23	0.83	0.85	2.61	+0.93	20.8	46.0	+20.6
23	11–15	5.6	85	52.5	0.48	3.20	4.07	+0.39	0.91	0.85	2.61	+0.85	20.9	46.0	+20.5
24	16–20	5.3	94	52.9	0.49	3.20	4.07	+0.38	1.03	0.85	2.61	+0.73	22.2	46.0	+19.2
25	21–25	6.9	93	53.7	0.48	3.13	4.07	+0.46	0.93	0.82	2.61	+0.86	21.7	46.0	+19.7
26	2/26–3/1	6.4	85	53.2	0.36	3.13	4.07	+0.58	1.01	0.82	2.61	+0.78	19.2	46.0	+22.2
27	3/ 2–6	7.0	80	53.6	0.45	3.13‡	4.07	+0.49	0.61	0.82‡	2.61	+1.18	20.2	46.0	+21.2
28	7–11	5.9	79	53.3	0.30	2.67	4.07	+1.10	0.79	0.81	2.61	+1.01	20.6	46.0	+20.8
29	12–16	6.0	71	53.5	0.26	2.67	4.07	+1.14	1.01	0.81	2.61	+0.79	20.3	46.0	+21.1
30	17–21	6.7	86	53.2	0.27	3.04	4.07	+0.76	1.16	0.78	2.61	+0.67	21.9	46.0	+19.6
31	22–26	5.8	77	53.0	0.28	3.04	4.07	+0.76	1.16	0.78	2.61	+0.67	21.7	46.0	+19.7
32	27–31	6.4	76	53.3	0.19	3.04	4.07	+0.84	1.00	0.78	2.61	+0.83	22.2	46.0	+19.2
33§	4/ 1–3	4.7	30	52.7	0.34	3.04	4.07	+0.69	1.09	0.78	2.61	+0.74	25.7	46.0	+15.7

* Fecal values were averaged in groups as follows: 1–4, 5–8, 9–12, 13–14, 15–18, 19–21, 22–24, 25–27, 28–29, 30–33.
§ Periods 6 and 33 were not 5-day periods, but 4- and 3-day periods respectively. The metabolic values were multiplied by 5/4 and 5/3 respectively.
‡ Fecal period lost; value used is average for periods 25 and 26.
† Nitrogen loss in feces was considered to be 10% of the intake, or 2.4 gm. for periods 1–14 and 4.6 gm. for periods 15–33.

of the skin, and *b*), purplish striae resulting from cracking of a friable skin.

(4) Easy bruisability, the result of atrophy of the walls of the blood vessels (4).

(5) Osteoporosis (not osteitis fibrosa as shown by normal serum phosphatase level).

(6) Apparent girdle obesity, which is more the result of a relaxed abdominal wall and crushed vertebrae than of actual fat.

Other features of the syndrome which are not particularly germane to the discussion are amenorrhea in women, impotence in men, hirsutism without other

TABLE 1(cont.) METABOLIC DATA ON CASE 1

Serum			Urinary excretion[1]		Treatment[1]	
Ca	P	P-tase	17-KS	Creat.	Est. Ben.	T.P.
mg.%	*mg.%*	*Bod. u*	*mg./ 24 hr.*	*mg./ 24 hr.*	*mg.*	*mg.*
8.7	2.3[I]	9.9[I]				
9.9[I]	2.5[I]	9.5[I]				
9.3[I]	2.5[I]	—				
10.4[V]	2.7[V]	9.2[V]				
			8.4[I]			
			13.5[II]			
10.4[I]	2.7[I]	8.2[I]			1.66[I]	
					1.66[IV]	
—	3.0[II]	6.8[II]			1.66[II]	
					1.66[V]	
					1.66[III]	
9.8[I]	2.8[I]	6.9[I]			1.66[I]	
					1.66[IV]	
					1.66[II]	
					1.66[V]	
10.0[I]	2.7[I]	6.6[I]			1.66[III]	
9.5[I]	3.1[I]	7.5[I]			1.66[I]	
					1.66[IV]	
10.4[III]	2.9[III]	8.3[III]			1.66[II]	
					1.66[V]	
9.8[I]	3.2[I]	4.8[I]			3.32[III]	
9.2[2]	3.0	2.9			3.32[I]	
					3.32[IV]	
10.5[II]	2.9[II]	4.1[II]				
			10.0[V]	678[V]		
			10.6[I]	605[I]		
			18.4[IV]	640[IV]		5×25
			17.2[IV]	635[IV]		5×25
			16.0[V]	700[V]		5×25
10.1[V]	3.2[V]	4.8[V]	19.8[IV]	714[IV]		5×25
			17.0[IV]	740[IV]		5×25
			15.6[V]	770[V]		5×25
						5×25
9.8[I]	3.2[I]	5.0[I]	17.0[II]	670[II]		5×25
			17.6[IV]	735[IV]		5×25[2]
						5×25[2]
			16.2[I]	690	5×1.66	5×25
9.7[III]	3.4[III]	10.5[III]	12.2[III]	625[III]	5×1.66	5×25
			11.0[IV]	754[IV]	5×1.66	5×25
					5×1.66	5×25
8.7[V]	3.2[V]	11.0[V3]			5×1.66	4×25

Est. Ben.=α estradiol benzoate; T.P.=testosterone propionate.

[1] Roman numerals indicate day of period to which values pertain.

[2] Thirty units daily of regular insulin was administered also.

[3] Patient was continued on testosterone propionate, 25 mg. every 2 days; serum phosphatase values continued to rise: 14.7 Bodansky u, April 13, 1940; 15.4 Bodansky u, June 6, 1940; 15.3 Bodansky u, June 15, 1940.

evidence of virilism, slight erythrocytosis, tendency to skin infections, hypertension and arteriosclerosis.

Long (9) and others have shown that the adrenal cortical hormone promotes gluconeogenesis, the conversion of proteins into sugar; and indeed, the diabetes of Cushing's syndrome has been attributed, rightly we believe, to a hypergluconeogenesis. Now, if proteins are being converted into sugar, not only will there be too much sugar, but also too little protein. Are not many of the features of Cushing's syndrome the result of protein shortage?

It would seem that, of those features listed above, numbers 2 through 6 could best be explained by protein deprivation, i.e., by a widespread tissue atrophy. The weak muscles, the thin skin, and the easy bruisability require no comment; osteoporosis, by definition, is the result of a lack of bone matrix, not of a primary disorder of calcium metabolism (10).

Woodyatt, (11) moreover, in a very acute case of Cushing's syndrome found a negative nitrogen balance, which remained negative in spite of a very high protein diet.

It was therefore decided that the goal to be sought in therapy was the establishment of a positive nitrogen balance. If this were accomplished and those manifestations thought to be the result of protein deficiency subsided, the hypothesis would be strengthened. The substance, par excellence, to promote a positive nitrogen balance is testosterone (12). Our data (table 1, 2, 3; fig. 1, 2, 3) show the results of such therapy on three female patients without adrenal cancer.

CASE HISTORIES

Case 1 (*M. G. H. 74372*, fig. 4) is a 25-year-old, single girl of Portuguese descent, who has been followed at the Massachusetts General Hospital for 5 years with the diagnosis of Cushing's syndrome. Her chief complaint when first seen was, "amenorrhea for 2 years."

She also revealed that she had been gaining weight about the face, neck and abdomen, and that her face had become ruddy and more hairy than before. In addition, she had noticed easy bruisability and had had recurrent skin infections.

On examination, she had the typical round, full, plethoric facies of Cushing's syndrome, with excessive facial and abdominal hair. The skin appeared atrophic with purplish striae and numerous visible dilated subcutaneous blood vessels. There were scars of old infections on the legs. The optic fundi showed some old hemorrhage and exudate. The heart was not enlarged. Blood pressure varied from 130 mm. to 170 mm. systolic, 80 mm. to 110 mm. diastolic. The clitoris was not enlarged.

Laboratory studies included: negative Hinton test result; R.B.C. 4.8; Hgb. 95% (T.); urine, a trace of albumen, occasional glycosuria, *B. coli* and *Staphylococcus albus* on culture; blood chemistry, not remarkable, sodium normal. Glucose tolerance test showed a failure to return to normal 4 hours after administration of glucose. Combined glucose and insulin test result paralleled that of the glucose tolerance test. Several B.M.R.'s were normal. Electrocardiogram showed evidence of myocardial damage. Follicle stimulating hormone assay on urine was negative

TABLE 2. METABOLIC DATA ON CASE 2

5-Day periods	Date	Urine vol.	Dried feces wt.	Wt. of pt.	Calcium				Phosphorus				Nitrogen†		
					Urine	Fecal	Intake	Balance	Urine	Fecal	Intake	Balance	Urine	Intake	Balahce
	1939	l.	gm.	kg.	gm.	gm.	gm.	gm.	gm.	gm.	gm.	gm.	gm.	gm.	gm.
1	9/30–10/4	7.5	63	53.8[I]	0.89	1.45	3.51	+1.17	1.88	0.87	2.94	+0.19	38.7	40.8	− 2.0
2	5–9	8.1	92	53.4[II]	0.80	2.52	3.51	+0.19	1.48	1.40	2.94	+0.06	37.2	40.8	− 0.5
3	10–14	8.2	68	53.7[IV]	0.79	2.04	3.51	+0.68	1.50	1.13	2.94	+0.31	37.5	40.8	− 0.8
4	15–19	8.0	136	—	0.82	3.55	3.51	−0.86	1.37	1.89	2.94	−0.32	34.2	40.8	+ 2.5
5	20–24	7.3	58	54.7[I]	0.73	1.68	3.51	+1.10	1.24	1.04	2.94	+0.66	37.9	40.8	− 1.2
6	25–29	6.8	78	54.4[III]	0.57	2.58	3.51	+0.36	1.18	1.49	2.94	+0.27	36.6	40.8	+ 0.1
7	30–11/3	9.1	110	55.4[IV]	0.73	3.51	3.51	−0.73	1.41	1.92	2.94	−0.39	40.5	40.8	−3.8
Studies were interrupted for 35 days because of skin infection which was treated with chemotherapy, x-ray and drainage. No hormone injections during the interim.															
8*	12/9–13	8.1	109	53.6[I]	1.19	4.60	4.24	−1.54	2.23	2.24	3.89	−0.58	57.8	68.4	+ 3.8
9	14–18	8.1	58	52.6[II]	1.00	2.64	4.24	+0.60	1.90	1.33	3.89	+0.66	54.1	68.4	+ 7.5
10	19–23	6.8	25	52.8[IV]	0.92	2.25	4.24	+1.07	1.66	1.15	3.89	+1.08	53.8	68.4	+ 7.8
11	24–28	6.0	76		0.83	3.93	4.24	−0.52	1.39	1.91	3.89	+0.59	49.4	68.4	+12.2
	1940														
12	29–1/2	5.4	92	53.6	0.72	5.15	4.24	−1.63	1.50	2.63	3.89	−0.24	42.8	68.4	+18.8
13	3–7	5.4	64	53.9[III]	0.77	2.72	4.24	+0.75	1.39	1.29	3.89	+1.21	50.3	68.4	+11.3
14	8–12	4.9	62	54.7[V]	0.64	5.13	4.24	−1.52	1.31	2.46	3.89	+0.12	48.1	68.4	+13.5
Studies were interrupted for 27 days. Patient went home. She received 25 mg. of testosterone propionate daily during the interim.															
15	2/8–12	4.3	—	57.5[II]	0.54	—	4.24	—	1.57	—	3.89	—	47.2	6.48	+14.4
16	13–17	4.8	63	58.6[IV]	0.43	2.85	4.24	+0.96	1.48	1.61	3.89	+0.80	46.7	68.4	+14.9
17	18–22	6.0	81	—	0.40	2.37	4.24	+1.47	1.41	1.30	3.89	+1.18	45.5	68.4	+16.1
18	23–27	5.7	110	59.2[I]	0.37	2.59	4.24	+1.28	1.42	1.45	3.89	+1.02	48.3	68.4	+13.3
19	28–3/3	5.3	—	58.9[III]	0.34	3.15	4.24	+0.75	1.90	1.80	3.89	+0.19	53.7	68.4	+ 7.9
20	4–8	5.7	125	56.3[V]	0.37	4.09	4.24	−0.22	2.72	2.32	3.89	−1.15	65.8	68.4	− 4.2
21	9–13	5.5	53		0.41	1.96	4.24	+1.87	2.66	1.13	3.89	+0.10	69.2	68.4	− 7.6
22	14–18	5.6	108	55.3[II]	0.40	4.21	4.24	−0.37	2.40	2.60	3.89	−1.11	67.7	68.4	− 6.1
No collections made for 30 days. Patient received 50 mg. daily of testosterone propionate from March 19 until April 20.															
23	4/20–24	5.4	64	57.7[V]	0.09	2.33	4.24	+1.82	1.39	1.38	3.89	+1.12	56.6	68.4	+ 5.0
24	25–29	5.5	69	—	0.10	2.95	4.24	+1.19	1.19	1.66	3.89	+1.04	46.4	68.4	+15.2
25	30–5/4	6.3	130	58.0[II]	0.14	4.50	4.24	−0.40	1.43	2.38	3.89	+0.08	57.7	68.4	+ 3.9
26	5–9	5.8	65	57.8[IV]	0.09	3.26	4.24	+0.89	1.40	1.77	3.89	+0.72	53.0	68.4	+ 8.6
27	10–14	4.5	39	58.3[V]	0.09	1.38	4.24	+2.77	1.40	0.71	3.89	+1.78	53.2	68.4	+ 8.4
28	15–19	4.9	44	—	0.07	2.72	4.24	+1.45	1.48	1.58	3.89	+0.83	52.5	68.4	+ 9.1
29	20–24	5.2	80	58.1[III]	0.09	3.53	4.24	+0.62	1.65	2.30	3.89	−0.06	55.5	68.4	+ 6.1
30	25–29	5.5	82	58.1[V]	0.11	1.89	4.24	+2.24	1.17	1.31	3.89	+1.41	46.7	68.4	+14.9
31	30–6/3	5.1	76	—	0.08	0.76	4.24	+3.40	1.20	0.48	3.89	+2.21	50.7	68.4	+10.9
32	4–8	5.0	62	57.6[II]	0.9	1.40	4.24	+2.75	1.40	0.99	3.89	+1.50	51.7	68.4	+ 9.9
33	9–13	6.6	174	58.8[IV]	0.10	2.62	4.24	+1.52	1.30	1.95	3.89	+0.64	53.2	68.4	+ 8.4
34	14–18	5.8	200	—	0.08	1.68	4.24	+2.48	1.23	1.39	3.89	+1.27	51.5	68.4	+10.1
35	19–23	5.9	173	58.9[I]	0.09	1.40	4.24	+2.75	1.12	1.34	3.89	+1.43	53.5	68.4	+ 8.1
36‡	24–27	5.5	30	58.5[III]	0.12	0.50	4.24	+3.62	1.22	0.47	3.89	+2.20	52.2	68.4	+ 9.4

* Urine collection for 1 day lost; metabolic values for remaining 4 days, multiplied by 5/4.
† 4-day period. Metabolic values multiplied by 5/4.
‡ Nitrogen loss in feces was considered to be 10% of the intake, or 4.1 gm. for period 1 to 7, 6.8 gm. for periods 8 to 36.

for 10 M.U. The 17-ketosteroids in the urine varied from 8 to 14 mg./24 hours before treatment. X-rays showed marked osteoporosis with numerous fractured vertebrae and bilateral kidney stones.

Both adrenals were explored. Biopsied sections were said to show no abnormalities. She received three courses of x-ray to the pituitary. There was a remission for about a year, with return of regular menses after the first course.

TABLE 2(cont). METABOLIC DATA ON CASE 2

Serum[1]			Urinary excretion[1]		Treatment[1]
Ca	P	P-tase	17-KS	Creat.	
mg.%	mg.%	Bod. U	mg./24 hr.	mg./24 hr.	mg. Est. Bn.
9.3[V]	2.8[V]	7.2[V]	17.2[V]	443[V]	3.32[II]
					3.32[IV]
			14.0[I]	428[I]	3.32[I]
					3.32[III]
			16.0[IV]	437[IV]	3.32[V]
			13.0[V]	483[V]	
					3.32[II]
					3.32[IV]
			10.3[I]	370[I]	3.32[I]
					3.32[II]
					3.32[V]
8.4[III]	1.7[III]	3.3[III]	18.4[IV]	540[IV]	
	2.5[2]	3.8[2]	15.0[I]	544[I]	
			18.5[V]		
			13.4[II]	412[II]	
			17[V]		
					T. P.
9.0[I]	2.9[I]	7.6[I]	26.4[IV]		5×25
			23.2[II]		5×25
9.4[I]	2.9[I]	9.3[I]	25.0[I]		5×25
					5×25
9.4[3]	2.8[3]	8.6[3]	37.0[III]		5×25
					5×25
9.0[I]	3.1[I]	8.0[I]	30.2[I]	670	5×25
			23.8[III]	592[III]	5×25
			18.6[V]	560[V]	5×25
9.5[I]	3.6[I]	12.4[I]			
			14.0[II]	510[II]	
			18.6[IV]	438[IV]	
			25.2[V]	608[V]	5×50
			24.2[V]	562[V]	5×50
			26.8[IV]	558[IV]	5×50
8.7[II]	3.3[II]	15.6[II]	22.4[V]	594[V]	5×25
			22.5[V]	590[V]	5×25
					5×25
9.7[I]	3.4[I]	24.9[I]	25.4[V]	670[V]	5×25
			17.8[V]	397[V]	5×25[4]
8.9[III]	3.6[III]	11.3[III]	21.6[V]	585[V]	5×25[4]
			11.6[V]	525[V]	5×25[4]
			13.6[V]	625[IV]	5×25[4]
9.1[I]	4.3[I]	12.2[I]			5×25[4]
			17.2[V]	594[V]	5×25[4]
8.3[IV]	3.9[IV]	15.7[IV]	24.0[IV]	654[IV]	4×25[4]

Est. Bn. = α estradiol benzoate; *V.P.* = testosterone propionate.
[1] Roman numerals indicate day of period to which values pertain.
[2] Values determined December 8.
[3] Values determined January 13.
[4] Vitamin D_2 (50,000 U) was administered daily also.

The last two courses had no effect. Kidney stones required operation twice.

She showed marked improvement on testosterone therapy, as discussed below. It is of real interest that after cessation of therapy, her improvement continued and it was found that the abnormality in sugar metabolism had entirely disappeared. Now, 6 months after cessation of therapy, her menses are normal and she presents no evidence of a recurrence.

Case 2 (*M. G. H.* 3397, fig. 5, 6, 7) is a 50-year-old native mother of 3 children, who has been followed at the Massachusetts General Hospital for the past 4½ years with the diagnosis of Cushing's syndrome. Her chief complaint when first seen was "marked weakness for 5 years."

She had had amenorrhea without hot flashes for 5 years; during this time she had noticed increasing facial and body hirsutism. Glycosuria had been noted 2 years before and treated with diet. She complained also of recurrent skin infections and brittleness of the nails. There had been a gradual weight loss of 86 lb. during the 4 years preceding her admission to the hospital.

On examination, she presented the typical plethoric appearance. The skin showed atrophy, striae, dilated subcutaneous vessels and easy bruisability. The optic fundi showed irregular arterioles, hemorrhage and exudate. The facial hirsutism was striking. The abdomen and breasts were flabby and pendulous. The heart was not enlarged. Blood pressure varied from 130 mm. to 160 mm. systolic, and 75 mm. to 100 mm. diastolic. The clitoris was not enlarged.

Extensive laboratory studies included: negative Hinton test result; R.B.C. varied from 4.1 to 5.5; Hgb. was 90 to 100% (T.); urine, no albumen, intermittent glycosuria. Blood chemistry values were not remarkable. Serum sodiums were 142 and 142.5 milliequivalents per liter. Glucose tolerance tests showed a failure to return to fasting level 4 hours after administration of glucose. Combined glucose and insulin tolerance tests paralleled these figures. The B.M.R. was normal. Follicle stimulating hormone assayed for 10 M.U. was weakly positive once, and negative twice; 17 ketosteroids in urine varied from 18 to 36 mg./24 hours. Electrocardiogram showed evidence of myocardial damage. X-rays showed extensive osteoporosis with numerous fractured vertebrae.

Both adrenals were explored. Biopsied specimens were not considered abnormal grossly or microscopically. She received two courses of x-ray treatment to the pituitary, and one course to the thymus without apparent effect.

She showed an amazing clinical improvement on testosterone therapy: walking a few steps without support after three years of complete invalidism in bed.

Case 3 (*M. G. H.* 234190) was a 43-year-old woman who had been followed by Dr. H. G. Brugsch at the Boston Dispensary for 6 years with classical Cushing's syndrome. Through Dr. Brugsch's courtesy we were enabled to carry on the investigations reported here.

A complete case history with autopsy findings will be reported later.

DISCUSSION

The administration of testosterone propionate resulted in a consistent alteration of the metabolic pattern in all three cases. After the administration of the drug there was a marked decrease in the nitrogen and phosphate excretions in the urine. The ratio of the

TABLE 3. METABOLIC DATA ON CASE 3

5-Day period		Urine Vol.	Dried Feces wt.	Calcium				Phosphorus				Nitrogen			
				Urine	Fecal	Intake	Balance	Urine	Fecal	Intake	Balance	Urine	10% of Int.	Intake	Balance
	1940	l.	gm.	gm.	gm.	gm.	gm.	gm.	gm.	gm.	gm.	gm.	gm.	gm.	gm.
1	8–12	5.8	73	1.13	3.10	4.11	−0.12	2.15	1.07	2.66	−0.56	43.9	5.2	51.9	− 2.8
2	13–17	7.3	118	1.07	2.73	4.11	+0.31	2.30	0.89	2.66	−0.53	51.3	5.2	51.9	+ 4.6
3	18–22	7.0	14	1.10	1.71	4.11	+1.30	2.21	0.65	2.66	−0.20	56.0	5.2	51.9	− 9.3
4	23–27	7.3	171	1.02	5.12	4.11	−2.03	1.90	1.92	2.66	−1.16	50.1	5.2	51.9	− 3.4
5	28–5/2	7.1	24	1.21	1.98	4.11	+0.92	2.25	1.56	2.66	−1.15	51.3	5.2	51.9	− 4.6
6	5/ 3–7	7.7	69	1.11	3.44	4.11	−0.44	1.86	1.44	2.66	−0.64	46.5	5.2	51.9	+ 0.2
7†	8–13	8.3	90	1.10	2.42	4.11	+0.59	1.73	1.07	2.66	−0.14	46.2	5.2	51.9	+ 0.5
8†	14–16	4.3	169	1.03	3.85	4.11	−0.77	1.61	1.76	2.66	−0.71	42.8	5.2	51.9	+ 3.9
9	18–22	8.9	34	0.99	2.48	4.11	+0.64	1.64	1.19	2.66	−0.17	44.2	5.2	51.9	+ 2.5
10	23–27	8.3	62	1.08	2.46	4.11	+0.57	1.64	1.22	2.56	−0.20	43.3	5.2	51.9	+ 3.4
11†	28–6/1	7.8	203	1.02	3.38	4.11	−0.29	1.60	1.76	2.66	−0.70	44.4	5.2	51.9	+ 2.3
12	6/ 2–6	8.4	61	0.85	2.80	4.11	+0.46	1.56	1.27	2.66	−0.17	42.5	5.2	51.9	+ 4.2
13	7–11	8.5	117	0.82	3.96	4.11	−0.67	1.20	1.80	2.66	−0.34	33.2	4.2	51.9	+13.5
14	12–16	7.1	108	0.79	3.52	4.11	−0.20	0.61	1.31	2.66	+0.74	26.5	5.2	51.9	+20.2
15	17–21	7.1	88	0.66	2.66	4.11	+0.79	0.57	0.99	2.66	+1.10	23.3	5.2	51.9	+23.4
16	22–26	5.8	77	0.60	3.14	4.11	+0.36	0.97	1.17	2.66	+0.52	27.6	5.2	51.9	+19.1

† Periods 7, 8, and 11 were not 5-day periods but 6, 3- and 4-day periods respectively. Metabolic data were multiplied by 5/6, 5/3, and 5/4 respectively.

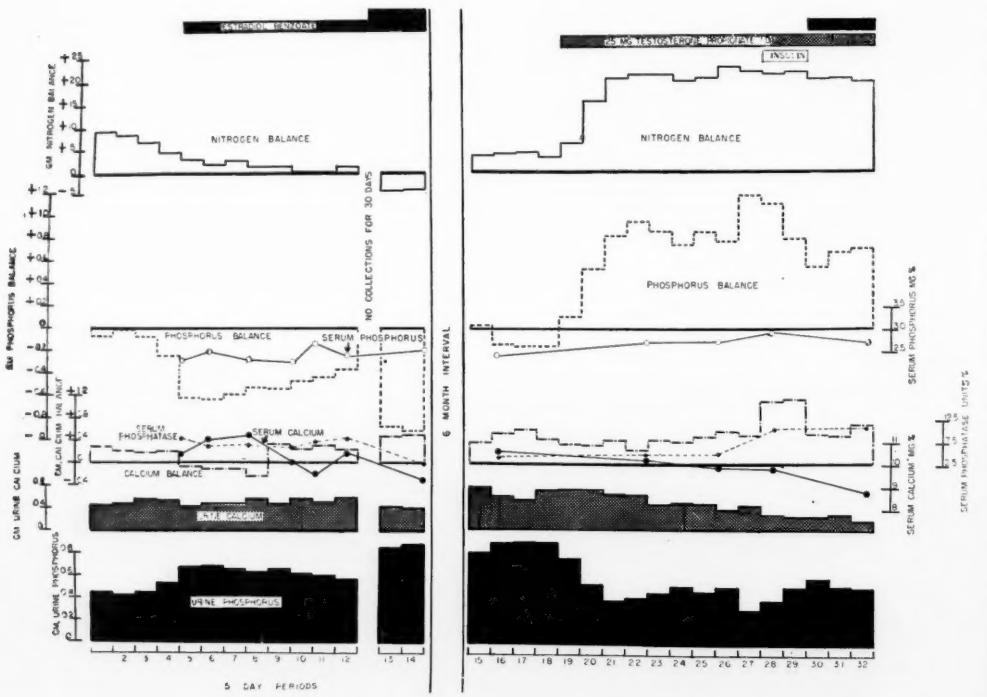

Fig. 1. NITROGEN, PHOSPHORUS AND CALCIUM METABOLIC DATA in *Case 1*, in relation to estradiol benzoate therapy, testosterone propionate therapy, testosterone propionate and insulin therapy, and estradiol benzoate and testosterone propionate therapy. In this, as in subsequent experiments, the patient was on the same low calcium diet throughout the experiment and for at least 5 days before metabolic collections were started; furthermore, the majority of the calcium intake came from added calcium gluconate rather than from the diet per se. In this, as in subsequent tables, the fecal values were averaged in groups of 2, 3 and 4 periods, a new group always being started at the time of a change in therapy. Since the ratio of calcium to phosphorus in bone is 2:1, the scale for the calcium balance has been chosen so that a fluctuation of 1 gm. of calcium will equal 0.5 gm. of phosphorus. The scale for the nitrogen balance is 1/20 that of the phosphorous balance, which is roughly of the order of magnitude of the ratio of nitrogen to phosphorus in protein, namely 17:1. The important findings are discussed in the text.

TABLE 3(cont.) METABOLIC DATA ON CASE 3

Serum[1]			Urinary excretion[1]		Treatment	
Ca	P	P-tase	17-KS[2]	Creat.	T.P.	Prog.
mg.%	mg.%	Bod. U	mg./24 hr.		mg.	mg.
10.5[I]	3.3[I]	4.5[I]				
10.3[V]	3.4[V]	6.2[V]				
			14.9[I]			
10.1[II]	3.3[II]	5.6[II]				
			15.2[IV]	900[IV]		5×10
9.9[V]	3.0[V]	5.4[V]	14.8[IV]	910[IV]		5×25
						3×25
			17.0[II]	768[II]		5×25
			14.8[I]			5×25
9.6[V]	3.4[V]	3.9[V]	13.0[I]	845[I]		5×25
						4×25
			16.6[II]	810[II]	5×25	
9.3[III]	3.0[III]	3.5[III]	9.4[IV]	700[IV]	5×25	
			11.2[V]	740[V]	5×25	
9.3[3]	2.5[3]	8.4[3]	16.0[V]	855[V]	5×25	

[1] Roman numerals indicate day of period to which values pertain.

[2] Values obtained before beginning balance experiments were as follows. April 4: 17-KS=11.5 mg./24 hr.; creatinine=925 mg./24 hr. April 5: 17-KS=11.8 mg.; creatinine=990 mg./24 hr.

[3] Value determined June 27th. T.P.=Testosterone propionate. Prog.=Progesterone.

change in nitrogen excretion to that in phosphorus excretion was approximately 17:1, the ratio of these substances in protein. The shift in the nitrogen balance was circa 20 gm. (= 125 gm. of protein) per 5-day period. According to Shohl (13), an adult body of 70 kg. contains about 2100 gm. of nitrogen. One may assume for our purposes, that an adult of 50 kg. will contain about 5/7 of this, or 1500 gm. of nitrogen. It will be seen, therefore, that, if one uses 1500 gm. for the amount of nitrogen in a normal female, these patients were retaining nitrogen at the rate of about 8% of the normal body nitrogen per month. In addition, there was a gradual decrease in the urinary calcium excretion. This trend persisted for weeks to months, at the end of which time the urinary calcium excretion was negligible. With the change in the urinary calcium excretion there was a gradual increase in calcium balance. After weeks to months, there was a delayed significant rise in the serum phosphatase. After cessation of testosterone propionate therapy the opposite changes in the same sequence resulted.

Associated with the metabolic changes there was an extraordinary change in the clinical picture. The patients all gained in weight and in strength; their abdomens became less protuberant, the skin became

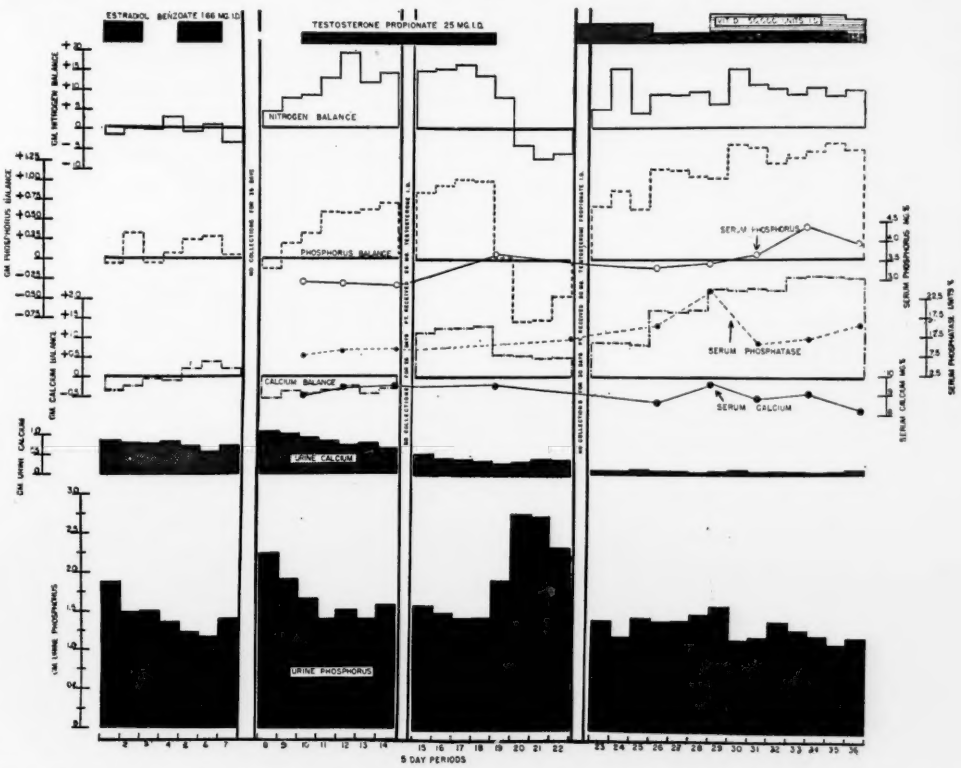

Fig. 2. NITROGEN, PHOSPHOROUS, AND CALCIUM METABOLIC DATA in *Case 2*, in relation to estradiol benzoate therapy, testosterone propionate therapy in two different doses, and vitamin D and testosterone propionate therapy. Details are the same as in figure 1.

noticeably thicker, with a disappearance of the reddish hue; they bruised less easily.

The above results, metabolic and clinical, at least suggest that testosterone overcomes the fundamental disorder in this disease; that is, decreases the hypergluconeogenesis. If that is true, the sequence of events following the administration of therapy may be as follows.

(*a*) Decreased gluconeogenesis
(*b*) Increased availability of amino acids
(*c*) Increased production of protein from amino acids with reduction of phosphate excretion
(*d*) Increased body tissues, notably skin, muscle, and bone matrix
(*e*) Increased serum phosphatase, an index of increased bone matrix formation
(*f*) Deposition of calcium and phosphorus into this bone matrix with resulting decreased urinary calcium excretion and increased calcium balance.

To recapitulate, the authors had an hypothesis concerning Cushing's syndrome; a series of experiments was set up to test this hypothesis; the expected results were obtained. This by no means establishes the hypothesis.

Fig. 4. Lateral view of *case* 1 showing that the so-called girdle obesity in this patient is the result of a relaxed protruding abdomen. Note also characteristic striae.

Furthermore, the hypothesis concerning Cushing's syndrome may be correct, but the explanation of the mechanism by which testosterone produces the beneficial effects may be incorrect. It may be that testosterone acts not by inhibiting gluconeogenesis but by promoting tissue growth. In favor of this second hypothesis is the fact that children with the adreno-genital syndrome (caused by an overproduction of testosterone or of some other steroid closely akin to testosterone) have somatic as well as sexual precocity. A third alternative is that testosterone may exert its effect by an inhibiting influence upon the pituitary. The possibility, of course, exists that those patients with Cushing's syndrome, who do not have adrenal cancer, have hyperadrenocorticism because of over-production of some pituitary corticotropic hormone. There is some evidence from these studies to favor this third hypothesis. Thus, in *case* 1 there was a complete remission, even to the extent of having a normal glucose tolerance test, after 2½ months of testosterone therapy; in *case* 3, the patient died of cerebral hemorrhage during her third month of therapy; at autopsy there was found a pituitary adenoma, the cells of which could not be classified. The authors wonder if the cells of the tumor may not have originally been basophil cells and may not have been in the process of alteration as the result of therapy.

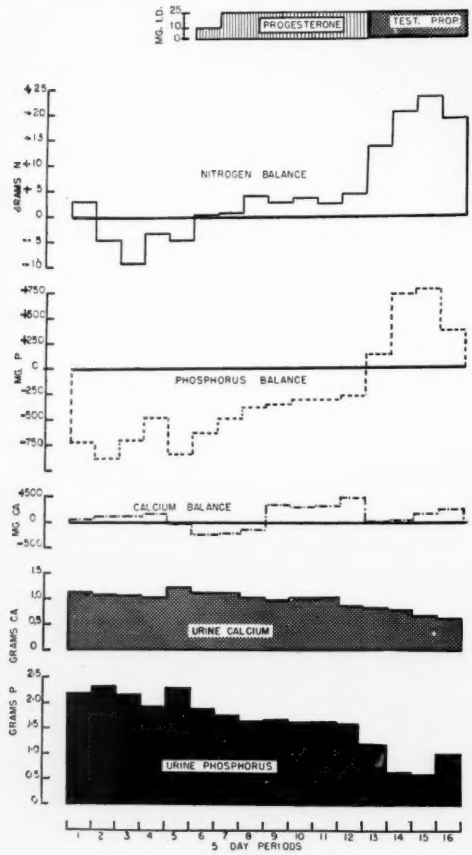

Fig. 3. Comparison of the effect of progesterone with testosterone propionate therapy in *case* 3 on the nitrogen phosphorous and calcium metabolic data. Details are the same as in figure 1.

SUMMARY AND CONCLUSIONS

To keep clear the distinction between facts and theories, facts are printed in italics.

1. Cushing's syndrome, whether the result of a cancer of the adrenal or otherwise, is associated with a hyperadrenocorticism.

2. The hyperadrenocorticism results in a hypergluconeogenesis.

3. The hypergluconeogenesis leads not only to an overproduction of sugar with decreased glucose tolerance, but to a decreased availability of amino acids with which to build protein.

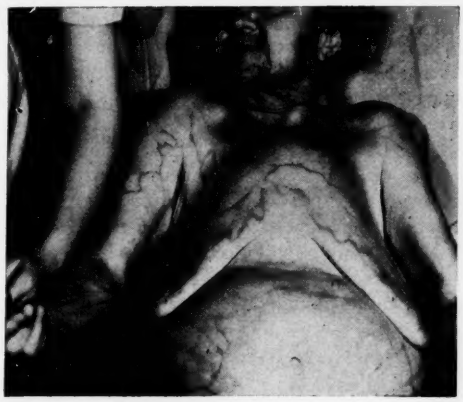

Fig. 5. INFRA RED PHOTOGRAPH OF *case* 2. Note thinness of skin as compared with control arm, relaxed abdominal wall, hirsutism of face and protuberance of sternum, the result of collapsed vertebrae.

4. Many of the clinical manifestations of Cushing's syndrome are the result of protein lack as exemplified by:

(*a*) Muscular weakness, with low creatinine excretion indicative of a decreased mass of muscle

(*b*) Thin skin, two manifestations of which are characteristic reddish hue resulting from transparency of the skin and purplish striae resulting from cracking of a friable skin

(*c*) Easy bruisability, the result of atrophy of the walls of blood vessels

(*d*) Osteoporosis, which by definition is the result of lack of bone matrix.

5. *Testosterone propionate therapy in 3 cases of Cushing's syndrome, without adrenal cancer, resulted in:*

(*a*) *Prompt retention of nitrogen, circa 20 gm. per 5 days*

(*b*) *Prompt retention of phosphorus, the ratio of retained nitrogen to retained phosphorus being approximately their ratio in protein*

(*c*) *A gradually decreasing urinary calcium excretion, with a gradually increasing calcium balance*

(*d*) *A delayed rise in serum phosphatase level, which is an index of bone matrix formation.*

6. *The above changes, (a) through (d), reversed themselves in the same sequence when therapy was discontinued in one of the patients.*

7. *Associated with the marked nitrogen retention were the following clinical changes:*

(*a*) *Increase in strength and weight*

(*b*) *Decrease in redness of the skin*

(*c*) *Loss of easy bruisability*

8. Three alternative hypotheses concerning the possible mode of action of testosterone are discussed:

(*a*) An inhibition of gluconeogenesis

(*b*) A stimulation to tissue growth

(*c*) An inhibitory effect on some pituitary corticotropic hormone.

ADDENDA

Certain observations were made in the course of these studies which do not directly concern the main thesis of this paper and were not presented before the Association for the Study of Internal Secretions, but which seem worth recording.

Estrin Therapy

Estrin therapy was tried in *cases* 1 and 2 because the osteoporosis in Cushing's syndrome is very similar to that seen in the postmenopausal state, and because it has been shown in this laboratory that estrin therapy has a markedly beneficial effect on the calcium balance in postmenopausal osteoporosis (10). Furthermore, estrin has been reported to have a beneficial clinical influence in Cushing's syndrome (14, 15). In figure 1 and table 1, it will be seen that estradiol benzoate therapy failed to exert a beneficial effect on the nitrogen, phosphorus or calcium balances in *case* 1. Indeed there is some suggestion that with larger doses there was a detrimental effect (see periods 13 and 14). Similarly negative results were obtained in

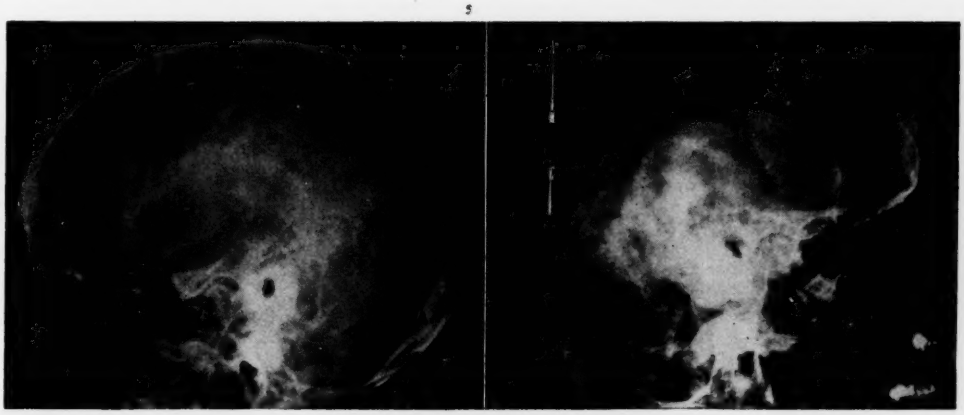

Fig. 6. LATERAL VIEW OF SKULL OF *case* 2 showing progression of characteristic decalcification. A, 1/20/37; B, 7/12/39.

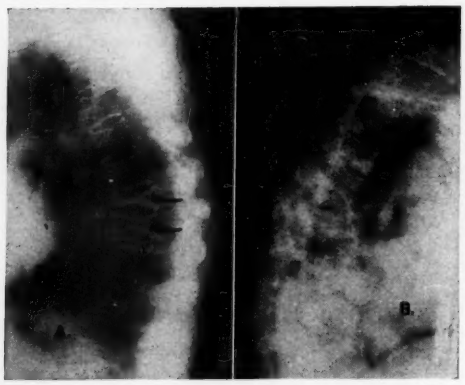

Fig. 7. LATERAL VIEW OF THORACIC SPINE OF *case 2*. A, 1/20/37; B. 7/12/39. Note two collapsed vertebrae in A, and note multiple fractures of all vertebrae in B, in spite of which patient was subsequently able to walk.

case 2 (fig. 2 and table 2), although here the data were less convincing because the patient had been on estradiol benzoate therapy before the studies were made, so there were no control periods.

Furthermore, in *case 1* estrin therapy in conjunction with testosterone therapy did not improve the effect of testosterone by itself (fig. 1, table 1, periods 30, 31, 32).

Progesterone Therapy

Since progesterone is chemically and biologically so closely related to testosterone, it was hoped it might have the same beneficial effect as testosterone. Accordingly, in *case 3* (fig. 3; table 3, periods 6–12), it was administered in the same milligram dosage as was subsequently used with testosterone. As will be seen, progesterone apparently did have a slight effect on the phosphorus and nitrogen balances, but very much less than that subsequently obtained with testosterone.

Vitamin D Therapy

The disorder in osteoporosis is thought to be a disorder of bone matrix formation and hence not a primary disorder of calcium metabolism. Since one of the main actions of vitamin D is to increase calcium absorption from the gastrointestinal tract, it seemed a priori very unlikely that this should have any beneficial effect where the bone disorder is the result of lack of bone matrix and not of lack of calcium. Nonetheless, in *case 2* the effect of vitamin D was tried (fig. 2; table 2, periods 29–36). It will be seen that the calcium balance did increase under the vitamin D therapy in conjunction with testosterone therapy. However, since the calcium balance was already increasing as the duration of testosterone therapy was prolonged, it is not clear from the experiment whether vitamin D altered the trend. Attention should be called to the extraordinarily large calcium balance at the end of the investigation in this case, circa 500 mg. a day, after 100 consecutive days of testosterone therapy and 40 days of vitamin D therapy.

Whether any importance should be attributed to the depression of serum phosphatase level after the administration of vitamin D therapy is problematical.

Additional Summary and Conclusions

Estradiol benzoate in 2 patients with Cushing's syndrome did not beneficially alter the nitrogen, phosphorus, or calcium balances; nor in conjunction with testosterone did it increase the beneficial effect attained with that agent alone.

Progesterone apparently had a slightly beneficial effect on the balances of nitrogen and phosphorus in one case of Cushing's syndrome, but milligram for milligram it was very much inferior to testosterone propionate in this respect.

Studies are reported in one case of Cushing's syndrome where vitamin D was given in conjunction with testosterone propionate; no conclusions are drawn.

Acknowledgement is made to the Schering Corporation, Bloomfield, N. J., for generous supplies of testosterone propionate (Oreton), alpha estradiol benzoate (Progynon-B) and progesterone (Proluton).

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ADRENAL CORTEX

THERAPEUTIC USE OF 'SODIUM FACTOR' OF ADRENAL CORTEX

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ONE OF THE MOST IMPORTANT FUNCTIONS of the suprarenal glands is the maintenance of the electrolyte equilibrium of the blood plasma, markedly modified in suprarenal insufficiency (Addison's disease) which is evidenced by natropenia, hypochloremia and hyperpotassemia. This electrolyte disequilibrium is in accord with the diminution of the blood volume, the increase in non-protein nitrogen and the diminution of the alkaline reserve in the blood. In 1939, Hartman (1) reported a substance, other than cortin, which was able to increase the sodium content of the blood plasma. In 1940 (2, 3), the same author and his coworkers claimed to have found in suprarenal extracts two separable and distinct substances: cortin, directly related to the vital function of the adrenal cortex, and a substance designated as Na factor (1), occurring in the cortex as well as in the medulla. The Na factor was considered to be responsible for the maintenance of the normal value of the sodium cation in the plasma. Its deficiency promotes the loss of sodium through the kidneys occurring in adrenal insufficiency. Hartman described the results obtained in his experimental work undertaken on adrenalectomized cats and dogs. He reached the following conclusions.

a) Adrenalectomized cats are maintained in apparently good condition by cortin alone; but the plasma sodium remains at levels characteristic of adrenal insufficiency.

b) Adrenalectomized cats can be kept alive on Na factor alone, but without the apparently good health of the animals treated with cortin. The level of the plasma sodium is in direct relation with the quantity of Na factor injected, increasing further when cortin is injected at the same time.

c) The Na factor acts by controlling the concentration of the plasma sodium but it does not exert a direct action on the levels of potassium, urea and glucose.

These experiments have interested us very much, since we consider that the availability of a substance capable of preventing loss of blood sodium is of extraordinary therapeutic value, not so much for the treatment of Addison's disease, but for therapy in a numerous group of morbid conditions, in which hyponatremia is an outstanding feature of the state of electrolyte impairment in the blood plasma.

The sodium cation plays an extraordinary role in regulating the electrolyte equilibrium in the blood plasma, as Giménez Díaz (4) has emphasized. The analysis of the experiments permits a deduction which is considered by us to be of fundamental importance. If we accept the existence of a substance of suprarenal origin, able to prevent the loss of plasma sodium, we must consider the lack of the renal function of base reserve and, in general, the hyponatremias as being directly or indirectly in relation to suprarenal insufficiency and, consequently, as constituting a condition to be treated with Na factor of the adrenal cortex.

Accordingly, we decided to try the application of the Na factor in clinical practice. The material was prepared by the Dominguez Laboratories of Buenos Aires according to Hartman's original technic; the differential solubility of the Na factor and cortin in certain organic neutral solvents having been taken into account as well as of their different tendencies to form colloidal solutions in water. Each cc. of the preparation employed contained the Na factor from 250 gm. of beef adrenals, prepared by previously described modifications of the original method. Small quantities of cortin were added to the preparation to increase its action as Hartman has suggested.

The indications for the use of the sodium factor, other than Addison's disease include: diabetes with acidosis and, especially, diabetic precoma and coma; nephritis and the so-called extrarenal uremias; different postoperative conditions (paralytic ileus, gastric dilatation, vomiting); shock; diarrheas; vomiting of pregnancy; intestinal obstruction; profuse perspiration; various intoxications; toxicosis and acetonemic vomiting of children; and edema. These indications for Na factor embrace in general the conditions in

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which exists the syndrome which Kerpel-Fronius (5) called "lack of salt." Furthermore, it would be indicated in the process in which there is no real hypochloremia but an increase in tissue chloride with hyponatremia. In all of these conditions, the fundamental factor is hyponatremia, since the picture does not get worse as long as the hypochloremia is not accompanied by hyponatremia (6).

Hartman's Na factor has been given by us to patients presenting a clinical picture in which natropenia acted as an important factor. The first cases treated are reported here.

Case 1. A woman patient had been splenectomized as treatment for hypersplenic anemia and hemolytic jaundice. The following day she was in a serious state to which an alkaline reserve of 39 vol.% CO_2 contributed. She was given an intravenous injection of 5 cc. of the Na factor solution. The next day the patient improved extraordinarily; the alkaline reserve had been raised to 59 vol.%, and the patient continued in excellent condition until she left the hospital.

Case 2. The patient, mother of a physician, was a diabetic in a precomatous state which did not disappear with the usual treatment; she was given two injections of 1 cc. each of the Na factor at an interval of 4 hours. Following the first injection, the patient began to recover her normal lucidity which she regained totally after the second injection.

Case 3. The patient was operated on for a postappendicular peritonitis. Since the second day after the operation and for approximately two weeks thereafter, she suffered from intractable vomiting and nausea which did not permit her to take food or to get rest. She was given 1 cc. of Na factor solution. The vomiting and nausea ceased quickly, she was able to retain food, her appetite returned and she was able to sleep. Her progress from then on was uneventful.

Cases 4, 5. These were also postoperative conditions with nausea and vomiting. These disturbances disappeared after one injection of 1 cc. of the Na factor solution. In both cases, the gastric troubles had lasted for more than one week.

Case 6. A patient, with renal lithiasis, had persistent vomiting on several occasions, which did not cease in spite of all the medications given. Each time, vomiting disappeared after the administration of Na factor.

Case 7. This patient had tuberculosis of the lungs and amyloid degeneration. Generalized edema was present, irreducible under the habitual treatments. With 3 injections of Na factor solution, the edema totally disappeared in the course of 3 days.

DISCUSSION

It is our opinion that the therapeutic administration of Hartman's Na factor of the adrenal cortex is of extraordinary interest and contributes to the understanding of the pathogenesis of a numerous group of morbid conditions in which primary or secondary suprarenal insufficiency exists as an exciting factor.

The number of cases in which Hartman's Na factor has been given is limited. We are also conscious of the fact that it is premature to speak about the real action of the preparation, since it has not been possible to carry out in all the cases determinations not only of the alkaline reserve, but also of sodium, potassium and chlorine of the blood plasma before and after the treatment. In spite of this we believe that the facts, supported by experimental investigations, are decidedly in favor of the clinical use of this preparation.

SUMMARY

The therapeutic value of the discovery made by Hartman and his coworkers of a substance, designated Na factor, extracted from the suprarenal glands, is pointed out. This substance provokes in adrenalectomized animals a marked elevation of the Na level of blood plasma. Because of the exceptional importance of the concentration of the sodium cation in the maintenance of the electrolyte equilibrium in the blood, a significant relationship is indicated between the hyponatremias observed in numerous morbid conditions other than Addison's disease and a primary or secondary suprarenal insufficiency. In accordance with this, a preparation of the Na factor was made and administered clinically with encouraging results in seven cases of various types.

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INSULIN RESISTANCE[1]

CRITICAL SURVEY OF THE LITERATURE WITH THE REPORT OF A CASE

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IN APRIL 1939, a patient with diabetes mellitus was admitted to the Los Angeles County General Hospital who was discovered to be insulin resistant and who subsequently died of diabetic acidosis. During the eleven dramatic days the patient was under our observation much effort was expended searching the literature for helpful suggestions for the treatment of the condition, while at the same time we attempted to carry on as intensive a study of our patient as was possible. Because of the rather chaotic state of current knowledge of this subject, we decided that a critical survey of the world literature with a report of our case might help clarify an important, even if comparatively rare situation. The term insulin resistance has been freely used since the discovery of insulin, but investigations published during the first eight or ten years following its introduction into therapeutics in 1922 have been more confusing than enlightening. Falta (1) was the first investigator to publish studies on insulin resistance and he devised a set of tests with intravenous insulin and rate of fall of the blood sugar whereby the presence or absence of this condition could be established. Radoslav (2), MacBryde (3), Monasterio (4, 5), Rimbaud (6), Norgaard and Thaysen (7), Labbé (8), Carrière, Gineste and Belbenoit (9) have elaborated or modified his methods.

In order to obtain a basis for discussion, we believe that the term insulin resistance should be well-defined. Two factors seem important: the element of time and the amount of insulin required. Both are important if we are to exclude from our discussion temporary changes in the diabetic status produced by such complications as coma, infection, etc. All students of diabetes are constantly confronted with the problem of meeting temporary demands for increased insulin dosage. For the purpose of our discussion such temporary changes, usually involving comparatively small increases of insulin, must be arbitrarily excluded.

As a starting point, we may use Root's (10) theoretical calculation of the daily insulin requirement of a completely depancreatized man. Employing values obtained on depancreatized dogs, Root estimated the insulin needs of such a man as between 200 and 300 U daily. A diabetic patient under certain conditions such as coma or infection may require even more insulin, but usually will respond to large doses by a fall in blood sugar in the course of 24 to 48 hours. We therefore choose to include in our definition of insulin resistance only those cases in whom after 48 hours observation, 200 or more units of insulin were required without an appreciable lowering of the blood sugar.

Under such a definition will be included cases of insulin resistance of both known and unknown etiology. This is in contradiction to the statement of Lawrence (11) who calls cases of known etiology "false insulin resistance." These factors known to cause insulin resistance are acidosis, infections, sepsis, overactivity of physiologic antagonists of the pancreas (pituitary, thyroid and adrenal secretions—the so-called extra-insular diabetes of Falta) and liver disease such as hemachromatosis. We emphasize that our definition is arbitrarily made on the combined bases of time and the amount of insulin.

PRESENTATION OF CASE

A. History

Present illness. The patient, a 53-year-old Jewish female, was admitted to the Diabetic Ward (Service of Dr. Strouse) of the Los Angeles County General Hospital on April 3, 1939. A known diabetic for 12 years, she

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[1] Synonyms: Insulin antagonism, insulin refractoriness and insulin insensitiveness.

was supposed to have been controlled on diet alone prior to 8 days before admission to the hospital. At this time her physician decided she needed insulin and prescribed 25 U of protamine zinc insulin every morning. Except for a brief period 3 years previously, prior to an operation (elsewhere), she had never received insulin. This insulin was regular insulin of unknown amount, from which she apparently had no ill effects. On April 1, 1939, 5 days after starting the use of protamine zinc insulin she developed pain in the front of the left chest which radiated to the base of the neck, "grabbing in character," associated with some shortness of breath. At the same time she noted a generalized itching rash which had persisted up to the time of entry to the hospital 2 days later.

Past history. An erythematous lesion of head and neck was treated at the Los Angeles County General Hospital Skin Clinic in 1935. No definite diagnosis was made at this time. The patient had also had frequent attacks of precordial pain associated with respiratory distress since 1935. A cholecystectomy and repair of a ventral hernia were performed in 1921, and a partial hysterectomy in 1935.

Menstrual history. No abnormalities were noted in the history. No record of the menopause was found.

Family history. No history of diabetes mellitus in the family was obtained.

Physical findings. The temperature was 100.2°F.; the pulse was 102 per minute and regular; the respirations were 22 per minute; and the blood pressure 122/72 mm. of Hg. The patient was a well-developed, fairly obese Jewish female who was conscious and rational, and who appeared to be in moderate distress due to pruritus from a generalized urticaria. The heart and lungs were normal on auscultation and percussion. No abnormalities were noted in the examination of the abdomen. A few shotty, non-tender glands were palpable in the neck and epitrochlear areas. Varicosities were present in both legs. There was a generalized urticaria, with many wheals on both arms, and a puffiness of the eyelids.

TABLE 1

Date	Intake	Insulin	Blood sugar	CO_2 Combining power	Fluid Intake	Fluid Output	Other laboratory findings
		U	*mg. %*	*vol. %*	Volume cc.		
4/3	10 cc. Ca gluc. i.v. Diet: Cal. 1360, C 100, P 60, F 80 H_2O per os	R25 s.c.	260		Not checked		Hb. 98%; W.B.C. 16,800; R.B.C. 5.0; P 82; L 14; M 4; E 2.
4/4	H_2O per os	R170 s.c.	370	28	4010	2450	
	2000 cc. Na lact. i.v.		408	32	+	+	
	1000 cc. 10% glucose in saline i.v.		317	24	H_2O per os	Pottenger suction	
	10 cc. Ca gluc. i.v.						
	1000 cc. Normal saline i.m.						
	Diet as above						
	Pottenger suction						
4/5	1000 cc. Normal saline i.v.	R70 s.c.	541	18	7260	4970	
	1000 cc. Hartman's sol. i.v.		417	8	+	+	
	3000 cc. Na lact.	R925 i.v.	408	15	H_2O per	Pottenger	
	10 cc. Ca gluc.		500	20	os	suction	N.P.N. 47
	500 cc. Blood and		417	13			
	500 cc. Citrate i.v.		385	18			
	1250 cc. 5% Na bicarb. (stomach tube)						
	H_2O per os						
4/6	2000 cc. 5% glucose i.v.	R1190 i.v.	500	18	9500	8550	N.P.N. 50
	3000 cc. Hartman's sol. i.v.		500	22	+	−	
	3000 cc. Na lact. i.v.		345	19	Ice		Creatinine 4.5
	1000 cc. Normal saline i.v.		400	42	chips		
	500 cc. 5% Na bicarb. per os		295	48			Urine alb. 0; mic. neg.
	H_2O per os. (ice chips)						
	Some nourishment						
4/7	3000 cc. Na lact. i.v.	R70 i.m.	247	48	5350	3865	Alb. 4
	2350 cc. H_2O per os	R135 i.m.	221	61			Glob. 2.9
	Some nourishment		294	60			Urine alb. trace
			286	60			Urinary diastase, normal
4/8	1000 cc. Na lact. i.v.	R275 i.m.	260	72	5705	6205	
	4705 cc. per os		292	68			
	Nourishment		303	54			
	C 101, P 68, F 59 (1207)		351	52			
4/9	3200 cc. Na lact. per os	R255 i.m.	274	55	6840	7680	
	3640 cc. H_2O per os		268	57			
	Nourishment		345	48			
	C 123, P 59, F 68 (1380)						

TABLE 1—*Continued*

Date	Intake	Insulin	Blood sugar	CO_2 Combining power	Fluid Intake	Fluid Output	Other laboratory findings
		U	*mg. %*	*vol. %*	Volume cc.		
4/10	3000 cc. Na lact. i.v.	R415 i.m.	265	55	7540	9715	
	1000 cc. Na lact. per os	R200 i.v.	305	48			
	3540 cc. H_2O per os		415	30			
			263	35			
4/11	1700 cc. Normal saline per os	R325 i.m.	317	33	11400	9075	N.P.N. 26
	4700 cc. H_2O per os	R380 i.v.	333	20			
	2000 cc. Na lact. i.v.	C500 i.v.	328	13			
	2000 cc. Normal saline, i.v.		241	13			
	1000 cc. 5% gluc. i.v.		333	13			
	Nourishment						
	C 103, P 57, F 68 (1252)						
4/12	9000 Normal saline i.v.	R100 i.v.	500	12	11645	1705	N.P.N. 33
	1000 cc. 5% gluc. i.v.	C1080 i.v.	455	15			
	625 5% Na bicarb. i.v.		400	—			Creatine 5.7
	1000 cc. Normal saline clysis		500	—			
	20 cc. Blood		420	13			Urine alb. 1+
	(Autogenous) i.m.		420	15			
			278	20			
			228	17			
4/13	500 cc. Na lact. per os	C40 i.m.	191	20	7440	1405	
	240 cc. Na bicarb. per os		225	28			
	2550 cc H_2O per os		272	28			
	4000 cc. Normal saline i.v.		330	33			
	150 cc. 50% sucrose i.v.		333	27			
4/14	150 cc. 50% Sucrose i.v.	C50 i.m.	364	24	475	840	Hb. 74%; W.B.C. 12,600; R.B.C. 3.9; P 88; L 10; M 2
	1 cc. Mercurpurin	C200 i.v.	513	32			
	325 cc. H_2O per os			38			
							Serum NaCl, 659; Na, 364 (normal 325); K, 27.4 (normal 15–21).
							Urine Na, 264 mg.; K, 104 mg./100 cc.

TOTAL 11-DAY PERIOD

Ca gluconate 30 cc.	R, i.m. and s.c.	1575	High 541	High 72
Na lactate 22,500 cc.	i.v.	2930	Low 191	Low 8
Normal saline 19,700 cc.		4505		
Hartman's solution 4000 cc.				
Na bicarb. i.v. 625	C, i.m.	90		
Blood transfusion 500 cc.	i.v.	1780		
		1870		
	Total	6375 U		

Ca gluc.=Calcium gluconate
C=Crystalline Insulin Units
R=Regular Insulin Units
i.v.=Intravenously
i.m.=Intramuscularly
s.c.=Subcutaneously

Course in hospital. (Refer to table 1 for details of laboratory work and therapy.) On admission, 4–3–39, the patient was considered to be a mild diabetic with a sensitivity to protamine zinc insulin, resulting in a generalized urticaria. She was put on a low carbohydrate, low calorie diet, 25 U of regular insulin, and calcium gluconate intravenously, for the urticaria. The next day, 4–4–39, it was apparent that her condition was more serious, as she had become restless, somewhat irrational, and the temperature had risen to 102.6°F. The blood sugar was 370 mg.% and the carbon dioxide combining power had fallen to 28 volumes %. The patient was given 170 U of insulin in divided doses and 3000 cc. of fluid intravenously.

Despite this therapy the blood sugar remained between 408 and 317 mg.% and the CO_2 combining power between 32 and 24 vol.%. An intradermal test with 0.1 cc. of protamine zinc insulin gave a large wheal in 15 minutes. Negative results were obtained with regular insulin (several brands) and with crystalline insulin.

On 4–5–39, the patient became semicomatose and vomited. Brownish fluid (1700 cc.) was obtained by gastric lavage. When aroused the patient complained of pain in the chest. An electrocardiogram was taken which showed a regular sinus rhythm, left axis deviation and no other findings of note. The blood pressure dropped from 120/60 to 80/60 mm. Hg, and the pulse became weak, thready, and rapid. A blood transfusion of 500 cc. was given with good response, the blood pressure rose to 120/70 and the pulse became full and bounding. Despite 70 U of regular insulin subcutaneously and 925 U of regular insulin intravenously (in divided doses) the blood sugar fall was slight, from 541 to 385 mg.%, and the CO_2 combining power fluctuated between 20 and 8 vol.%. Fluid, 5000 cc., was given intravenously. At this time it was appreciated that the patient was insulin resistant.

On 4–6–39, 1190 U of regular insulin and 9000 cc. of fluids were given intravenously. The urticaria had disappeared. The patient remained semicomatose, but showed a general improvement towards evening. The blood pressure remained 120/70 mm. Hg.

On 4–7–39, the patient was remarkably improved, appeared rational, alert, and began to eat well. Because of the marked improvement the insulin dose was decreased to 205 U of regular insulin intramuscularly for the 24-hour period and 3000 cc. of fluid intravenously. With this regimen the blood sugar fluctuated between 221 and 294 mg. %, and the CO_2 combining power rose from 48 to 60 vol. %.

On 4–8–39, lesions characteristic of herpes simplex appeared in the throat and the patient complained of abdominal pain. Her appetite was poor. From this time until her death 6 days later the course was steadily downhill, despite large doses of insulin and continued supportive treatment. On this day 275 U of regular insulin, in divided doses, was given intramuscularly and 1000 cc. of intravenous fluid. The blood sugar rose from 260 to 351 mg. % and the CO_2 combining power fell from 72 to 52 vol. %.

On 4–9–39, she complained of severe, continuous left chest pain, not related to breathing and she vomited. The blood sugar fluctuated between 274 and 345 mg. % and the CO_2 combining power varied from 48 to 55 vol. %. Regular insulin, 255 U, was given intramuscularly in divided doses.

On 4–10–39, increasing restlessness was noted and the general condition appeared definitely worse. She continued to complain of chest pain and nausea. Because of the increase in signs and symptoms the 24-hour insulin dosage was increased to 415 U of regular insulin intramuscularly and 200 U intravenously, in divided doses. Fluid, 3000 cc., was given intravenously. The blood sugar fluctuated between 263 and 415 mg. % and the CO_2 combining power fell from 55 to 30 vol. %.

On 4–11–39, the patient continued to be restless. Despite 5000 cc. of fluids intravenously and 325 U of regular insulin intramuscularly, 380 U intravenously and 500 U of crystalline insulin intravenously, in divided doses, the CO_2 combining power fell from 33 vol. % to 13 vol. %, and the blood sugar fluctuated between 241 and 333 mg. %. A second electrocardiogram showed definite changes: there was now a downward deflection of the major complex in lead 3; lead 4f showed a small "S" wave, an upright "T" wave, and a prolonged RT interval.

On 4–12–39, it became difficult to arouse the patient who showed increasing hyperpnea. Slight edema of the ankles and hands was noted. The temperature rose to 102.6° F. Despite 10,625 cc. of fluids intravenously the CO_2 combining power fluctuated between 12 and 20 vol. %. During the morning despite 100 U of regular insulin intravenously and 1080 U of crystalline insulin intravenously the blood sugar remained between 500 and 420 mg. %. Because of this apparent lack of response to insulin it was decided to stop insulin to see what the effect would be on the blood sugar. This was done at 1:30 P.M. The blood pressure remained at 130/70 mm. of Hg.

On 4–13–39, the next morning, the blood sugar was 191 mg. % and the CO_2 combining power was 20 vol. %, but the clinical condition was much worse. Increasing edema of the legs and sacrum was noted, and many moist rales were heard at both lung bases. The temperature remained 102.6°F. Insulin was resumed at 5:00 P.M., 40 U of crystalline insulin was given intramuscularly. During the 24 hours 4000 cc. of normal saline were given intravenously. The blood sugar rose from 191 to 333 mg. %, while the CO_2 combining power rose from 20 to 33 vol. %.

On 4–14–39, the patient appeared moribund. There was a generalized edema. Signs interpreted as bronchopneumonia appeared at the right lung base. Fifty U of crystalline insulin was given intramuscularly, and 200 U intravenously, in divided doses. The blood sugar rose from 364 to 513 mg. % and the CO_2 combining power rose from 24 to 38 vol. %. Oxygen, mercupurin, and intravenous sucrose were used as last resorts, but to no avail. The patient died at 12:10 P.M.

B. Autopsy

An autopsy was made 21 hours after death by Dr. George Fein. Examination of the head was not permitted.

Heart. The organ weighed 430 gm. The musculature was extremely pale and flabby. All chambers were dilated. There was a mild degree of atherosclerosis of the coronary arteries but no occlusion was found. Microscopic section revealed a severe grade of fragmentation and atrophy of the muscle fibers.

Respiratory system. The left pleural cavity contained 400 cc. and the right pleural cavity 500 cc. of a clear, straw-colored fluid. The left lung weighed 520 gm., and the right lung 560 gm. Both lower lobes posteriorly showed atelectasis. The parenchyma was congested and an increased amount of frothy red fluid could be expressed from the cut surfaces. Microscopic sections revealed atelectasis. There was no evidence of pneumonic consolidation.

Digestive system. There was marked generalized ileus. Numerous fibrinous adhesions extended between the anterior surface of the colon, anterior abdominal wall and the omentum. The most dependent portion of the cecum was thinned out and there was a local collection of fibrin on the peritoneal surface of the cecum. There was 500 cc. of cloudy, rather foul smelling material in the peritoneal cavity from which was cultured hemolytic streptococcus and *Escherichia coli.*

Pancreas. The organ weighed 120 gm. and was grossly normal. Microscopic section revealed advanced necrosis of the island cells with hyalinization of capillaries and areas of fat necrosis.

Hepatic system. The liver weighed 2050 gm. The parenchyma was flabby and the lobular architecture was obscured. There was evident cloudy swelling and yellow mottling suggestive of fatty change. Microscopic section revealed the liver cells shrunken and atrophic with large sinusoids. Glycogen was very sparingly distributed.

Kidneys. The kidneys together weighed 600 gm. On the anterior surface of the upper pole of the right kidney was a nodular mass beneath the capsule which measured 6 × 9 cm. and which did not communicate with the adrenal. Cut section revealed the mass to be composed of golden-brown tumor tissue divided by fibrous strands. The kidneys were large, swollen and pale. The capsule stripped without difficulty. Microscopic section of the tumor revealed many groups of polyhedral cells with clear staining cytoplasm separated by fibrotic strands. Microscopic section of the kidney revealed marked degeneration of tubules with cloudy swelling and necrosis of tubular epithelium.

Genital system. The ovaries were small and wrinkled.

Endocrine system. The adrenals together weighed 25 gm. and were grossly normal. Microscopic section revealed marked necrosis of the cortical cells with brown pigmentation within the cell membranes. No nuclei were visible. (Postmortem change) The medullary cells stained well. The pituitary, thyroid and parathyroid glands were not examined.

Anatomical diagnoses. 1. Necrosis of islands of Langerhans; 2. Acute, local peritonitis; 3. Paralytic ileus; 4. Myocardial degeneration with dilatation and congestive failure; 5. Pulmonary atelectasis; 6. Hypernephroma.

Following the autopsy the Severity Index, according to the method of Rabinowitch, (12) was calculated to be 19 (severe) (table 2).

TABLE 2

Factor	*This case*	*Severity index rating*
Age	52	4
Duration of coma	None until terminally	0
Degrees of unconsciousness	Semi-conscious	2
Coffee ground vomitus	No	0
Infection	Peritonitis, terminal (autopsy)	3
Blood pressure	120/70 to 80/60 mm. Hg	1
Plasma CO_2 combining power	8	3
Non-protein nitrogen	50	1
Associated conditions	Urticaria with insulin resistance	5
		19
Clinical stage	*Severity index*	
Very mild	5	
Mild	6–10	
Moderately severe	11–15	
Severe	16–20	
Very severe	21 plus	
CASE PRESENTED	19	SEVERE

C. Experimental Work

Several studies were carried out in an effort to uncover the mechanism of our patient's resistance to insulin. The skin tests showed an allergic response to protamine zinc insulin, but not to other insulins. The patient's serum was studied for (1) an anti-insulin effect, (2) passive transfer of insulin, (3) antigenic substances antagonistic to insulin and (4) allergic antibodies to insulin.

Study of patient's serum for; (1) anti-insulin effect, and (2) passive transfer of insulin. Four and a half cc. of the patient's serum and 4.5 cc. of non-diabetic control serum were each incubated for 3 days with 20 U of insulin. The patient's serum plus insulin and the control serum plus insulin mixtures were then injected into separate rabbits, each of which had been fasted for 3 days. The fall in blood sugar was comparable in the two cases, demonstrating no anti-insulin substance in the patient's serum.

Although the patient had received 1000 U of insulin intravenously in 8 hours before the blood was withdrawn for the test, there was only a slightly greater fall than the control serum. This test was not carried out long enough, however, to determine whether there was a passive transfer of any large amount of insulin in the patient's serum.

(3) *Study of patient's serum for antigenic substance antagonistic to insulin.* Blood, taken from patient's heart just after death, was kept in a refrigerator 1 week. Serum was removed just before test. Blood clotted immediately after withdrawal, there was no hemolysis. Patient was given 200 U of crystalline insulin intravenously within 3 to 4 hours of death.

Five cc. of the patient's serum was injected intravenously into a fasted rabbit on 4–21–39. This had no appreciable effect on the blood sugar which was followed for 3 hours. On 4–22–39 the same rabbit was given 20 U of insulin intravenously and the blood sugar fell from 133 to 32 mg. % in two hours. The blood sugar level was restored with intravenous glucose. The rabbit was fasted from 4–25–39 to 4–28–39. In the afternoon of 4–27–39 the rabbit was injected intravenously with 6 cc. of the patient's serum. The next morning 20 U of insulin was given intravenously producing convulsions in 2 hours. The rabbit died during the following night and autopsy showed no gross lesions of note.

These tests demonstrated that there was no antigenic substance in patient's serum antagonistic to insulin, as no anti-insulin effect was produced in the rabbit's blood. The criticism is valid, however, that the blood which was used was obtained just at the time of death and was refrigerated for one week before use.

(4). *Study of patient's serum for allergic antibodies to insulin.*

(a) *Prausnitz-Küstner (13) passive transfer test.* ½ cc. serum of patient was injected intradermally in right arm of diabetic patient—area marked. ½ cc. of serum of control (non-diabetic) injected intradermally in left arm of same diabetic patient—area marked.

In 24 hours 10 U of insulin injected at marked sites—both arms. A positive reaction is indicated by redness, itching, or wheal formation at the site of injection. Occasionally a generalized urticarial reaction occurs.

A very faint erythema was obtained with patient's serum. The control was negative.

(b) Test for precipitins to insulin following technic of Karr, Scull, and Petty (14), except that U40 insulin instead of U20 insulin was used.

Insulin was used as an antigen in dilutions of 1/20 to 1/640. The patient's serum, normal serum, a diabetic's serum and a saline control were tested for precipitins with the above dilutions of insulin. The results obtained could not be interpreted because the controls gave such high degrees of precipitation.

DISCUSSION OF OUR CASE

The precipitating factor in our case was apparently the patient's hypersensitivity to protamine zinc insulin which produced a generalized urticaria. Despite the fact that these lesions cleared completely in 3 days, following the cessation of protamine zinc insulin and the administration of calcium gluconate, the expected response to crystalline insulin or to regular insulin was not forthcoming. In effect, we were as helpless in treating diabetic acidosis as were the physicians of the pre-insulin era. Our patient's history of the development of an itching, erythematous lesion of the head and neck three years earlier is of interest in suggesting an allergic background, although the condition was not diagnosed as an allergic manifestation. We do know that the early lesion was not caused by protamine zinc insulin.

Infection as a cause of insulin resistance is frequently encountered although the resistant phase is usually transient. A diabetic in diabetic acidosis from whatever cause almost invariably requires more insulin during the first hours of treatment than he will need after control is established. At autopsy our patient had local peritonitis about the cecum, a condition unsuspected during life and one which we believe developed shortly before death. The incidental finding of a small hypernephroma further complicates the picture, although there is little likelihood that it was related in any way to the insulin resistance.

In retrospect it will be noted that on the second day following admission to the hospital 995 U of insulin and on the next day 1190 U were used. At this time the blood sugar dropped from 541 to 295 mg. %, the CO_2 combining power rose from 18 to 48 volumes %. The next day only 205 U of insulin were necessary to maintain the blood sugar between 221 and 294 mg. % while the CO_2 combining power steadily rose to 60 vol. %. At this point we felt that we had control of the situation, but within 48 hours discovered that the daily administration of 275 and 255 U of insulin was insufficient, as the blood sugar slowly rose and the carbon dioxide combining power diminished. It is of course possible that had we had an appreciation of the significance of the association of an allergic state with insulin resistance and had continued massive doses of insulin during these two critical days, we might have averted the fatal termination.

Glen and Eaton (15), in reporting their case of insulin resistance, partially outlined the important factors in the causation of this syndrome. Efforts were made in our case to follow these suggestions, which are listed on the opposite page, paralleled by other reported work.

REVIEW OF CASES REPORTED IN THE LITERATURE

In reviewing the many cases in the literature reported as examples of insulin resistance we were confronted with the difficulty of selecting those cases which fell into our arbitrary classification and definition. As already mentioned, immediately after the discovery of insulin many case reports were published as examples of insulin resistance, which were in fact, merely temporary changes in insulin needs to a greater or lesser extent. The transition from such cases to those adhering to our definition cannot be

Reported Observations	Results in Our Case
Is Lack of Response Due to Sensitivity to a Particular Brand of Insulin?	
Several cases are reported which show a normal response following change to insulin prepared from a different animal source or the use of crystalline insulin. Herold (16) reports a case sensitive to the polypeptide of insulin itself which was successfully treated by a prolonged course of desensitization.	The intracutaneous wheal test was positive only for protamine zinc insulin and negative for all other insulins, including crystalline insulin.
Is Lack of Response Due to Lack of Absorption?	
This might develop from injections given into indurated skin at the site of injection. A change to the intramuscular or intravenous route eliminates this possibility. Insulin also has been found not to be taken up by the cells (17).	Insulin was given intravenously with no more effect than subcutaneously.
Is Lack of Response Due to Absence of Some Other Factor?	
Identical or related substances with enzyme-like properties are thought necessary for the activation of insulin and the conversion of glucose to glycogen. These are variously named: *Insulin-complement* (18), a substance found in fresh muscle having the ability to decrease the optical rotary power of glucose. *Glycomutine* (19), another substance, an enzyme, found in fresh muscle, capable of transforming glucose into a reactive form. *Insuline* (20), an hypoglycemic substance found in the tissues, even in a depancreatized dog, and necessary for the activation of insulin. *Phosphatese* (21), an enzyme necessary in the intermediary metabolism of the liver. *Co-enzyme* (11).	This factor was not thoroughly investigated in our case due to obvious technical difficulties of procedure. Just before the patient's death sodium diphosphate was given intravenously, because of the striking results shown by Glen and Eaton (15), but this was tried too late for fair interpretation. As there are no commercial or purified materials corresponding with these substances, therapeutic trial with them in insulin resistance is impossible. It is also equally impossible to test for their absence, as is understandable from their nature.
Is Lack of Response Due to Neutralization of Insulin?	
(1) By destruction	
This is a possibility as suggested by the work of many (17, 22, 23). Even after large doses in resistant cases no insulin can be recovered from the urine. A recent report (24) shows that massive doses given to rabbits cannot be recovered from the blood after 60–90 minutes, suggesting storage in other tissues, because the hypoglycemia persisted over a much longer period.	General tests for contra-insulin substances gave negative results. We obtained insufficient evidence on this point. Blood taken after 1000 U of insulin intravenously, during several hours preceding showed only slightly more effect on lowering the blood sugar of the experimental animal than normal serum, both incubated with 20 U of insulin.
(2) By combination	
In sensitive individuals, insulin as a polypeptide, may act as an antigen thus producing insulin antibodies (14). These authors demonstrated a precipitin reaction with the serum of an insulin resistant diabetic and insulin used as the antigen. The presence of insulin antibodies may also be demonstrated by the Prausnitz-Küstner passive transfer test (13). This is particularly true in insulin allergy (25).	No information of significance was obtained since the precipitin test showed more positivity with the normal control serums than the test serum. Attempts to produce allergic antibodies in a rabbit by the use of the patient's serum were unsuccessful. The Prausnitz-Küstner (13) test was negative.
(3) By antagonism	
In 2 insulin-resistant cases (26, 27), no excess of pituitary diabetogenic hormone was found in the urine, although the antagonistic effect of the thyroid, adrenal and anterior pituitary has been well established by Houssay (28, 29) and others. Beneficial effects have followed pituitary irradiation in several instances (30). Estrogenic substances have been shown to alter the course of experimental diabetes by depressing the pituitary diabetogenic fraction in dogs (31), in monkeys (32) and in human beings (33). Collens et al. (34) were unable to produce this effect in man. However, estrogens were apparently effective in the resistant case of Glen and Eaton (15). Moore (35) considered adrenal antagonism. Forrest (36) reported 5 diabetics who ran lower blood sugars when receiving parathyroid extract by mouth along with their insulin, than with insulin alone in the same dosage. He found no effect with the parathyroid extract alone. Serio (37) reported inhibition of insulin action by thyroxin in a diabetic with hyperthyroidism.	Assay of the urine for various hormonal constituents, particularly the pituitary fractions, would have been valuable, but we were unable to do so. Furthermore, the hypophysis was not obtained at autopsy. A fair trial with estrogens was not obtained in our case.

TABLE 3.—SUMMARY OF CASES REPORTED IN THE LITERATURE

Number of Case Sex and Age Author	1 Male 52 Root (10)	2 Female young Glassberg (38)	3 Female 55 Allan (39)	4 Male 58 Wiener (27)	5 Female 38 Marble (26)	6 Male ? Mason (40)	7 Male 58 Allan (41)	8 Female 58 Karr (14)	9 Female 65 Thannhauser (42)	10 ? Murphy (25)	11 ? Murphy (25)	12 ? Engel (43)	13 Male 24 Ulrich (44)
Duration of diabetes	?	4 years	12 years	3 years	5 years	2 years	5 years	5 years	6 years	?	?	?	4 years
Allergic history	0	0	0	0	Eosinophilia	?	?	—	Asthma?	Urticaria	Asthma	—	None
Previous insulin allergy	0	Local reaction	0	0	? due to large amounts of insulin	?	?	Local reactions urticaria	?	?	?	?	?
Other endocrine disturbances	—	—	—	? Absence of pituitary diabetogenic hormone			—	—	—	—	—	—	Acromegaly
Precipitating factors	?	Generalized urticaria	Generalized urticaria	Pyelitis	Rheumatoid arthritis	Infection of biliary tract	Infection of biliary tract	? Angina	?	?	?	Hemochromatosis	?
Type of insulin used during resistance	?	Beef & pig Regular	Regular & crystalline	Regular & protamine Zn	All types	?	?	All types	?	Sensitive to all	Sensitive to all	?	?
24 hr. insulin Before resist. During resist.	? 1680 (Total)	20–40 317 (26,965 in 3 mo.)	15–20 500	? 3250	100 240–675	? 200–400 (2,075 in 24 hr. before death)	? 200–1000	? 600 (146,559 in 20 mo.	90 1060 i.v. 170(H)	? ?	? ?	? 1365	30 360
After resist.	—	104	—	440	240–675	—	—	None	—	—	—	None	None
Other therapeutic measures		Parathyroid ext. with fall of blood sugar			X-ray to pituitary: no improvement		Synthalin B		Dietary restriction				
Results of therapy	Death	Control	Death	Fair control, still studying	Requires same dose still studying	Death delayed hypoglycemia	Death	Recovery	Death (?) 12 Days	Recovery	Recovery	Death	Spontaneous remissions 3 attacks
Lab. findings: 1) Blood sugar High Low			536 385	325 75				200	950 395			502 —	500 87
2) CO_2 Vol. % High Low			54.4 6.0	64 9					Coma			Coma	
Experimental findings	1) No contra-insulin substance in blood	1) No contra-insulin substance in blood 2) Positive insulin complement (Phosphatase)		1) No Contra-insulin substance in blood 2) No passive transfer of insulin	1) Insensitive to Himsworth's glucose-insulin test. No diabetogenic AP hormone in urine		1) No contra-insulin substance in blood 2) No passive transfer 3) No insulin complement lack	1) No contra-insulin substance in blood 2) Passive transfer 3) + precipitin		No passive transfer	No passive transfer		
Theories as to etiology	Hemochromatosis	?	?	?	? relation of hepatomegaly and splenomegaly	Cyst in midbrain (Autopsy)	Hemochromatosis	Cured with rabbit serum sensitized by patient's blood	? Liver	?	?	Hemochromatosis	Acromegaly

TABLE 3— *Continued*

Number of Case Sex and Age Author	14 Female 44 Wayburn (45)	15 Female 65 Rudy (46)	16 Female 58 Hills (47)	17 Male 17 Lawrence (11)	18 Female 48 Glen (15)	19 Male 66 Clay (48)	20 Male 72 Mohler (49)	21 Male 25 Labbé (50)	22 Female 60 Cannavo (51)	23 Female 12 Sztavrovsky (52)	24 Male 59 Labbé (53)	25 Male 26 Claar (54)	26 Male 52 Labbé (55)
Duration of diabetes	5 years	?	3 years	2 years	9 years	2 years	12 years	?	?	2 months	few weeks	3 years	
Allergic history	None	0	0	High eosinophilia	0	0	0	0	0	0	0	0	0
Previous insulin allergy	?	0	0	0	0	0	0	0	0	0	0	0	0
Other endocrine disturbances	—	—	Hyperthyroidism	0	—	—	—	—	0	0	0	0	0
Precipitating factors	Pulmonary tuberculosis	Urticaria	Exacerbation of hyperthyroidism	?	? Hysterectomy and unilateral oophorectomy	Upper respiratory infection	Pulmonary tuberculosis with hemorrhage	?	Sarcoma of toe, radiotherapy, sepsis	?	Gangrene toe, pulmonary infection	? Two previous attacks of jaundice	Infection, hemochromatosis
Type of insulin used during resistance	?	?	?	?	?	Regular	Regular	?	?	?	?	?	?
24 hr. insulin requirement u: Before resist. During resist. After resist.	 92 415 —	 5 515 None	 30 200–890 —	 40 220 Still resistant	 ? 950–1050 (Daily for 27 days) —	 None 960 —	 0–30 1150 (Daily for 4 mo.) —	 ? 730 and 140 (In 48 hours) —	 None 50–1050 —	 None 300 ?	 20 340–490 —	 None 70–900 —	 50 720 —
Other therapeutic measures			Iodides		i.v. Phosphate and estrogen given with improvement					Controlled on synthalin, but toxic effects			
Results of therapy	Death	Recovery	Still resistant	Still resistant	Death	Death	Death	Death	Death	Improved with synthalin	Death	? Recovery	Death
Lab. findings: 1) Blood sugar High Low	 282 (only 1 reported)	 410 72	 520 48	 379 54	 1500 117	 408 290	 440 105	N.P.N. 77	 406 ?	 240 ?	 495 ?	 370 215	Urea N 55 348 262
2) CO_2 Vol. % High Low	Coma	47 47	75 10		Terminal acidosis	45	59	64 11.6			20 12.6	43 14	22
Experimental findings					Insulin antagonism in rabbits with patient's serum				No contrainsulin substance in blood. No passive transfer. No insulin antibodies. No lack of insulin complement	No contrainsulin substance in blood. No passive transfer. No insulin antibodies. No lack of insulin complement			
Theories as to etiology	Pulmonary tuberculosis, liver damage	? Precipitated by impurities in insulin	? Relation to hyperthyroidism	? Lack of coenzyme	? Related to pituitary — as some pituitary abnormality at autopsy	?	? Lack of some substance	? Relation of liver disease: (Hepatomegaly with fatty degeneration)	Sepsis	?	Infection	Hemochromatosis	Hemochromatosis, pituitary pathology

a heavy dividing line, but we found it necessary to use such a line. Therefore, in table 3 we list only those examples of insulin resistance which lasted 48 hours or longer and which required 200 U or more of insulin daily. References to important cases which do not fulfill our criteria of insulin resistance will be found in the bibliography (3, 51, 56–68, 104).

The cases listed in table 3 may be summarized from an etiological point of view into five groups:

1. *Disturbance of endocrine glands:* 5 cases [2 pituitary (40, 51), 1 acromegaly (44), 1 hyperthyroid (47), 1 ovarian deficiency (15)].

2. *Infection:* 5 cases [pyelitis (27), sepsis (49, 51, 53, 55), pulmonary tuberculosis (45)].

3. *Hepatic disorders:* 5 cases (10, 41, 43, 50, 54).

4. *Diseases of the skin and allergy:* 8 cases [5 urticaria (14, 25, 38, 39, 46), 1 rheumatic arthritis with eosinophilia (26), 1 eosinophilia of undetermined etiology (11), 1 bronchial asthma (42)].

5. *Unexplained:* 2 cases (48, 52).

THEORIES AS TO THE PATHOGENESIS OF INSULIN RESISTANCE

Many factors contribute to the great complexity of the problem, particularly the possibility of pluriglandular antagonism or acceleration of insulin action, and the complicated role played by the liver in the control of the blood sugar level. Rarely, in all probability, is one factor predominant, but for the purposes of discussion, single factors will be summarized separately.

1) *The Endocrine System. a) Hypophysis.* The fact that the pituitary gland is an antagonist of the pancreas has been amply confirmed since Houssay's original studies (69). Young (70) has recently summarized the subject of the relationship of the separate fractions of the anterior pituitary to carbohydrate metabolism. Many have stressed the relation of increased pituitary activity and consequent insulin antagonism. Cases have been reported (30, 51, 61, 71) in which pituitary irradiation has produced striking changes in the amount of insulin required. However, without proof of pituitary disease the results of pituitary irradiation must be accepted with reserve as spontaneous relief of insulin resistance does occur. The antagonistic effect on insulin following the injection of blood from elderly, obese patients into rabbits has been reported as due to a pituitary factor (72), but these results have not been confirmed by others (73).

b) Thyroid. Abnormal sugar metabolism may occur in hyperthyroidism without the presence of diabetes mellitus. The antagonistic effect of hyperthyroidism and thyroxin on diabetes mellitus and insulin has been demonstrated experimentally and clinically (37, 74).

c) Ovary. The role of the estrogenic hormone in insulin resistance is not settled and the experimental results have been variable (15, 31–34).

d) Adrenal. A discussion of the interrelation between the adrenal and the pituitary glands is not within the scope of this paper, but it has been summarized by Long (75). The possibility of hyperactivity of the adrenals in a case of insulin resistance has been suggested (35).

e) Parathyroid. Experimental evidence (36, 38) has shown that parathyroid extract apparently intensifies insulin action, but no clinical correlation has been made.

2) *Infection.* During infection the insulin requirement of a diabetic may increase. The cause of this increased resistance in some cases and not in others is not understood. Suggestive factors have been reported by several investigators. Fever has been shown to cause a rise in insulin requirement (76, 77, 78). Pus may inhibit insulin action (65). Toxins have been suggested as inhibitors of insulin action in two ways, by stimulation of the thyroid and adrenal glands (79), and by liver damage (80, 81). Other workers have noted a toxic effect caused by bacterial proteins (82). Aubertin (83) in a valuable review of insulin resistance (1936) summarized additional studies on this topic.

3) *Liver.* The role of the liver in carbohydrate metabolism is exceedingly complex; glycogen storage or failure of this function caused by hemachromatosis, fatty deposition, necrosis or some unknown factors; the detoxifying function; the production of an insulin activating enzyme and a host of other considerations have been studied by many other investigators (9, 42, 50, 76, 80, 81, 84–90).

4) *Allergy.* We have been impressed with the frequency with which this factor has been mentioned in association with insulin resistance. Rudy (46) believes the resistance may be caused by a blockage of insulin in the affected skin. Foerster's case (59) with generalized urticaria was cured by stopping insulin, a procedure which might be advisable in the absence of severe ketosis. (Other references 16, 25, 38, 58, 89, 91, 92, 93.)

5) *Other Factors.* This group consists of scattered observations on both man and animals from which valuable information may come in the future, although the results are difficult to interpret now. These include the effect of the acid-base balance (15, 21, 94–101), enzymes (11), inorganic phosphates (15, 21, 100, 101) vitamin B (102) and type of carbohydrate fed (57, 103).

TREATMENT

The first step in the treatment of a case of insulin resistance is to evaluate the etiologic factors responsible for the condition and attempt to eliminate them as rapidly as possible. Specifically, one should test for insulin sensitivity and change the type and brand and route of administration if necessary. Perhaps the form of insulin least likely to produce allergy is the crystalline insulin. Most evidence seems to indicate that there is not necessarily any upper limit to the number of units of insulin which may be given and our opinion agrees with that expressed by Taussig (22), who wrote, "The fact that enormous doses of insulin were finally effective can readily be explained by the law of mass action of inorganic chemistry, which, to a certain extent, is valid also in enzymatic and immunological reactions."

General therapeutic measures should be directed against all the possible contributory factors in the production of insulin resistance, such as infections

(including syphilis), hyperthyroidism, pituitary dysfunction, and allergic states, as well as the usual nonspecific supportive treatment employed in relieving diabetic acidosis. Other measures worthy of empiric trial because of successful use by others include endocrine therapy (estrogenic preparations, parathyroid extract); intravenous phosphate solutions; change in type of carbohydrate in the diet; vitamin B; pituitary irradiation; and desensitization.

SUMMARY

Insulin resistance, for the purpose of this paper, has been defined as a condition occurring in a patient who, after 48 hours of observation fails to show an appreciable lowering of the blood sugar following the administration of 200 U of more of insulin per diem. These criteria have been adopted in order to eliminate the temporary resistant phase commonly encountered in the treatment of diabetic acidosis.

We present a case of insulin resistance, apparently precipitated by hypersensitivity to protamine zinc insulin. This patient took 6,375 U of insulin in 11 days, with 1,205 U as the highest 24-hour amount. A discussion of the experimental procedures now available for the study of insulin resistance is given (insulin antibodies, anti-insulin substance in the blood, increase in the insulin antagonists, such as pituitary diabetogenic fraction, indirect evidence of lack of insulin complement).

All of the cases we could find in the world literature, fulfilling our criteria, are tabulated in detail, with a discussion of significant features.

Insulin resistance is discussed from the standpoint of pathogenic factors (endocrine, infection, liver, allergy, tissue inactivity and acid-base balance).

An outline for treatment is presented.

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INSULIN RESISTANCE

ASSOCIATION OF EXTREME INSULIN RESISTANCE WITH ALLERGY. REPORT OF A CASE.

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VARIATIONS in the response to exogenous insulin is a commonly noted occurrence in the diabetic. It may be found, within certain limits, at some time or another, in practically every individual suffering from a low sugar tolerance. Cases are occasionally encountered, however, with extreme resistance to insulin in which enormous amounts must be given before a balance is effected. Such cases, according to Marble (1) are not very common. He found two in 11,500 cases of diabetes registered at the Joslin Clinic since the introduction of insulin in 1922. The severest example on record was reported by Wiener (2). The patient, a known mild diabetic, for no apparent reason developed an acute severe imbalance with acidosis. For 3 weeks at home his insulin was raised gradually to 260 U in 24 hours without results. On the tenth hospital day he was cleared of acetone after daily insulin doses of 400, 1105, 900, 900, 900, 900, 900, 1500 and 2700 U. The highest dose, 3250 U, was given on the 14th hospital day. He was discharged after 6½ weeks with a daily intake of 1700 U. Eight months later he was controlled on 440 U a day.

There has been no adequate explanation as yet for this form of metabolic upset. The cases reported in the literature are associated with a long list of variegated conditions and several well studied ones fail to show any apparent cause.

The following case of severe insulin resistance is presented because it occurred in a patient with a 35-year history of asthma, it was associated with local and general allergic reactions to the insulin, and it returned to such a mild state in 7 weeks that 10 U of insulin caused shocks.

CASE REPORT

A. L., a male Hungarian, age 60, a fruit dealer and a former champion wrestler, was in excellent health up to July, 1939. At that time he developed nocturia, polyuria and excessive thirst. A physician diagnosed the condition as diabetes. Protamine zinc insulin was given in gradually increasing doses but without much effect on the urinary sugar. By the 24th of November the protamine Zn insulin dose had reached 70 U, a rigid diet was being observed, and the urine still showed a 4+ sugar reaction. He was then advised to go into a hospital and on November 25 he entered the Metabolic ward of the New York City Hospital, Welfare Island.

On entrance he was a well-developed, cooperative, ambulant male. Except for a hernia the physical examination result was negative. He gave a history of bronchial asthma for 35 years although there was no evidence of it any time in the hospital.

His initial blood sugar was 445 mg.% and the urine gave a 4+ reaction for sugar and for acetone. He was put on a diet of C 150, P 75, and F 67. From 4 P.M. till 12 midnight he was given 120 U of regular insulin. Because there was no improvement the dose was increased the second day so that 870 U was given in the 24 hours. On the 3rd day with his condition still severe 920 U was injected. On the 4th day the urine became acetone-free, for the first time, and on that day he received 400 U of insulin. From then on the dose of insulin was gradually reduced until the end of the 7th week when all insulin was stopped. It was noted at that time he was having shocks on 10 U.

Following the first dose of regular insulin there was a general as well as a local allergic reaction. This lasted 4 days and was of sufficient severity to require several injections of adrenalin.

Other laboratory findings were N.P.N. 34, blood cholesterol 200 and blood chlorides 456 mg.%. Serum albumen was 2.6 and serum globulin 2%. The B.M.R. was −3 and −2%, and the blood Wassermann test result was negative. The E.K.G. was essentially normal. On January 21, 7 days after the insulin was stopped, a glucose-tolerance test gave blood sugar values of 63, 89, 133, 238, 170 mg.%.

Painstaking examinations were made throughout the patient's stay in the hospital for possible focal infections without result. He was discharged January

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29, 1940, on a diet of C 152, P 96, F 108, no insulin. The urine was sugar-free, and he was in otherwise excellent physical condition. He returned for a check-up on September 30, 1940. At that time he was in good health and gave a history of a normal life since he left the hospital. During that time, 8 months, he kept on a slightly modified diet with no insulin. A glucose-tolerance test gave blood sugar values of 125, 174, 236, 250, 95 mg.%. There was a spill of 1+ sugar in his urine during the test.

DISCUSSION

It will be noted that this patient was a known diabetic for over 13 weeks before he entered the hospital. Likewise the great majority of extreme insulin resistant cases reported in the literature have been known diabetics for some time before the insulin resistance appeared. From this one might say that the condition occurs only in diabetics and that it is not so much a form of diabetes as it is a complication of that disease. Furthermore, all other characteristics of diabetes are present: the onset is typical of any precomatose state in the diabetic, the blood sugar rises to the average precoma height, 445 mg.% in our patient; the urine is found to contain 4+ sugar with acetone and possibly diacetic acid; and the blood may eventually show definite evidences of acidosis with low CO_2 combining values. Insulin in large enough doses will reverse this process until a balance is accomplished and even shock will occur with an overdose. Finally, as in the usual type of diabetes, insulin tolerance improves under regulation, the patient goes on with a diabetic existence, and the sugar tolerance curves remain typically diabetic in form.

If we agree with Root (3) that the pancreas produces, at the maximum, 300 U of insulin a day, which seems reasonable, we are forced to consider the presence of some factor in these cases that inactivates both the endogenous and the exogenous insulin. The condition cannot be a state of true resistance in the full sense of the word as insulin rarely, if ever, fails to have its effect if the dose is great enough. It cannot be a lack of insulin 'activator' as successful balancing comes from increased insulin and not from any added 'activating substance.' Furthermore it has been proven that insulin was not lost in the urine. We are, therefore, left with the possibility of the presence of some insulin inactivating factor.

An explanation may be found in changes in some organ itself or in some product of that organ. Extreme insulin resistance has been found in association with diseases of a number of organs. Yet it is a rare complication in any one of these diseases as, for example, hemochromatosis. Also there is a gradually increasing group of cases in which no organ in the body can be found abnormal. Hence it is difficult to say from the evidence presented that any one organ can be held responsible. Possibly the product of some organ is in excess. This might be the anti-insulin or diabetogenic factor of the pituitary.

Infection commonly causes a moderate insulin resistance but this is by no means true with every infection. Few if any of the extreme insulin-resistant cases on record could be attributed to an infection. Wiener's patient responded normally to a typical infection reaction 4 months before he entered the hospital for insulin resistance. There was no history or sign of infection on his second admission. In Allan and Constam's (4) patient several weeks after insulin tolerance became normal the patient contracted an upper respiratory infection that lasted 8 days. This did not bring about a recurrence of the insulin resistance.

Allergy may be a factor in insulin resistance. A number of cases have been reported to date in which the evidence points strongly to such a possibility. Any of the forms of insulin including the crystalline may produce allergic reactions. Glassberg (5) thought it was due to the insulin radical itself because it occurred with both the beef and pork varieties. Foerester (6) quoted a case of diabetes with urticaria and acidosis in which the acidosis became worse on increasing the insulin and quick improvement followed its cessation. Karr (7) noted in his patient that all kinds of insulin produced a reaction. Skin tests showed the patient to be sensitive to the insulin itself. By using a sensitized rabbit serum he was able to desensitize this woman and produced a marked improvement in the insulin resistance.

Apparently it is only the patient with generalized allergy or urticaria that develops unusual insulin resistance. This was noted by several authors but was brought out strongly by Glassberg who had the opportunity of studying his patient 9 months before the insulin insensitiveness appeared. At this first observation the patient was sensitive to insulin, giving only local reactions. There was a normal carbohydrate response to the insulin and in a short time spontaneous desensitization occurred. On the second admission the patient was again sensitive to insulin but exhibited a marked urticaria. At this time the severe insulin resistance was present. We have found allergic reactions to insulin very rare and this is the first case in our experience in which generalized urticaria was encountered.

The case presented here can be considered one of extreme insulin resistance. He was a known diabetic for some months before his hospitalization. Up to the time diabetes was found he was an unusually healthy individual and entered the hospital without signs of

any complicating condition. Except for asthma for 35 years, there was nothing in his history that was abnormal. There was no error on his part such as breaking diet or suddenly dropping his insulin. There was likewise no evidence of infection on admission or during his stay in the hospital. The only abnormality recognized was a generalized severe urticarial reaction to the insulin. This disappeared spontaneously in a few days, at the same time, incidentally, that the acetone left the urine. The condition responded to insulin when a sufficient amount was given and could be considered a temporary state as the patient was able to leave the hospital in 2 months on a liberal diet without insulin.

SUMMARY

A case of extreme insulin resistance is presented. Such a condition may be considered of relatively rare occurrence. Apparently it is found only in diabetes and can be held a complication rather than a special variety of the disease. The etiology is by no means clear. There may be no abnormality recognizable other than diabetes. There is evidence, however, to show that some insulin antagonistic factor is present in the system; that it equalizes all the endogenous and large quantities of the exogenous insulin; that it can be overcome if large enough doses of insulin are given; and that its presence in the body is temporary. The close association of a generalized allergic reaction to insulin in this case offers a possible etiologic factor.

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ASTHMA, DIABETES MELLITUS AND HYPERINSULINISM

HYPERINSULINISM

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THE LITERATURE of the past decade is replete with reports that asthmatics have a tendency to hypoglycemia. Black (1) found more than half of a large series of asthmatic patients to have low fasting blood sugar levels and increased glucose tolerance (low glucose tolerance curves). Ohler, in a personal communication to Joslin (2), said that he found low glucose tolerance curves in 14 asthmatics. Wilmer, Miller and Beardwood (3), Malone (4) and Waldbott and his collaborators (5) made similar observations.

If hypoglycemia is an essential factor conditioning the appearance of asthmatic seizures in sensitive individuals, we should expect such attacks to be absent, or, at most, very rare in diabetics. Kern (6) has shown that although diabetes mellitus and bronchial asthma often share a common heredity they are to some extent mutually exclusive, both diseases occurring very frequently in members of the same family but only extremely rarely in the same person. He postulated a genetic relationship between the two conditions and assumed that they were due to a defect in the same gene that can take one of two directions. According to him, diabetes is the recessive and allergy the dominant variation. Joslin was formerly impressed with the rarity of asthma in diabetics and had but 6 cases among the 7,000 or so reported (2). Later, he stated (7) that he had seen 12 additional cases among a large number (not given) of diabetics. More recently, he states (8) that "the usual belief that diabetes and allergy seldom occur in the same patient [is true] only if the phrase 'at the same time' was added." Apparently, he still feels that the concomitant occurrence of the two diseases is rare.

On the other hand, Swern (9) found but 6 diabetics among more than 4,000 allergic patients. Walker is quoted by Joslin (2) as having seen but 2 diabetics among some 3,000 asthmatic patients. The first case of diabetes seen by Rackeman, who had a very extensive allergic practice, was sent to him by Joslin (2). Wilmer, Miller and Beardwood (3) had only 2 diabetics among almost 5,000 allergic patients. Indeed, two of Joslin's patients [*1112* (10) and *17701* (8)] had asthma first and the attacks ceased altogether when diabetes was superimposed. Sensitivity to ragweed disappeared in another patient (2382) when the diabetes began, but the hay fever persisted despite the development of diabetes (10).

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Asthma is frequently associated with hypothyroidism. Levi and Rothschild (11) found that many cases could be benefited by feeding thyroid extract. They felt that the therapeutic value of iodides for bronchial asthma could be attributed to an increase in thyroid activity. Byron (personal communication) states that he has determined the basal metabolic rates of many asthmatics and that these rates are usually low. He recalls one example of a patient, with bronchial asthma, in whom the attacks ceased completely when hyperthyroidism developed. After thyroidectomy, the asthmatic attacks returned in an intractable form. The aggravating effect of hyperthyroidism on diabetes mellitus is too well known to require comment.

Lately, Rusk and his associates (12) have demonstrated a relation between allergic attacks, such as asthma and urticaria, and serum potassium. They found high serum potassium levels in asthmatics and the concentration took a sharp rise just before and during allergic attacks. Experiments now in progress show fairly low serum potassium values in diabetics. When serum potassium was determined in parallel with glucose tolerance tests, the potassium fell as the glucose rose following the ingestion of sugar and then both substances tended to return to their initial concentrations. One of Rusk's experiments (his No. 5) shows this same phenomenon.

Rusk claimed that asthmatic attacks could be prevented by feeding potassium chloride. This therapeutic effect has not been confirmed by other investigators (13). He also demonstrated that attacks could be induced by feeding large amounts of sodium chloride. Sandstead and Beams (14) administered large amounts of sodium chloride to diabetics and found that their patients could take more liberal diets with actual reduction in insulin dosage. This has been confirmed (15). Thus, sodium chloride, which has an aggravating effect on asthma, apparently makes diabetes milder.

These considerations point to a reciprocal relation between asthma and diabetes. It is generally accepted that diabetes is due to a deficiency in insulin secretion, or hypoinsulinism. It therefore seems logical to assume, purely as a working hypothesis, that asthmatics, who are opposite to diabetics in so many respects, have a surfeit of the hormone, or have hyperinsulinism. This hypothesis was tested in a number of patients suffering from attacks of bronchial asthma on an allergic basis. In all the work cited above, the glucose tolerance tests were carried out for the usual 2 or 3 hours. Harris (16) has shown that it is necessary, in order to reach a definite conclusion as to the

diagnosis of hyperinsulinism, to carry out the glucose determinations for 6 or even 8 hours.

During the summer of 1939, 9 patients with seasonal asthma all of whom gave positive skin reactions for pollens, and 3 with perennial asthma with positive skin reactions for foods and other common allergens, were subjected to the longer glucose tolerance test. Each patient was given 200 cc. of 50% glucose, flavored with lemon juice, to drink after the fasting blood sugar level had been determined. The blood glucose was then determined at hourly intervals until the patient had symptoms of asthma. The test was then terminated by giving the patient a glass of milk. In each case, the asthmatic attacks stopped within 15 minutes after the breaking of the fast. Three of the patients (who had very low initial blood glucose levels) had symptoms at the beginning of the test. These symptoms cleared up soon after the administration of the glucose and reappeared with the fall in blood sugar. The glucose tolerance curves are given in table 1. All determinations were made by the Folin-Wu micro method. Values are in mg. of glucose per 100 cc. of blood. The patients had symptoms of asthma at the times indicated by asterisks.

TABLE 1

Patient	Fasting	Hours after ingesting 100 gm. of glucose						
		1	2	3	4	5	6	7
Seasonal (hay fever) cases								
1	64*	132	97	82	70	56*		
2	80	150	87	80	69	58*		
3	110	144	118	96	84	73	66	51*
4	64*	90	79	69	56*			
5	118	152	120	102	83	72	64*	
6	98	142	100	82	69	62	54*	
7	98	138	106	78	61*			
8	105	152	102	83	76	67	58	48*
9	88	136	92	82	76	70	62*	
Perennial cases (bronchial asthma)								
10	65	136	110	88	72	65	61*	
11	125	144	109	86	76	58*		
12	59*	110	94	83	71	65	57*	

It is interesting to compare these figures with those reported by Rusk (12) and referred to above: fasting, 79 mg.%; ½ hour after ingestion of 100 gm. of glucose, 120 mg.%; one hour, 118; 1½ hours, 127; 2 hours, 126; 3 hours, 107; 4 hours, 53 mg.%.

These 12 patients, all of whom suffered from asthmatic attacks, thus had glucose tolerance curves that warrant the diagnosis of hyperinsulinism. This suggests a therapeutic test. If the hyperinsulinism is corrected by appropriate treatment, amelioration of symptoms would be further evidence that the endocrine disturbance plays a part in the genesis of the attacks. The patients were therefore given Harris's diet for hyperinsulinism (17). This is a low carbohydrate, high fat diet with the food divided into frequent small meals.[1] Quickly absorbable carbohydrates, such as sugar, candy, cake and the richer vegetables (potatoes), are avoided. This is done to prevent any sudden rise in blood sugar which is the stimulus to insulin secretion. The over generous production of insulin in patients with hyperinsulinism would induce a state of hypoglycemia which it is our aim to prevent. Caffeine, which raises the level of the blood sugar rather suddenly (18), is proscribed for the same reason. The large amount of fat in the diet depresses the activity of the islet cells. This diet is the opposite of the low fat, high carbohydrate diets now used for diabetes to stimulate the sluggish insulin production. The food is given in small amounts at frequent intervals for two reasons. The small increments of sugar added to the blood by digestion of the carbohydrates enable the patient to absorb energy at a rate slow enough to avoid stimulation of insulin production. The short intervals enable the patient to replenish the blood sugar before any marked postprandial drop can take place. The blood glucose level is thus kept between normal limits.

The first 5 of these patients had tried potassium chloride (5 grains, 3 times a day, orally) for a few weeks without any relief. The results of the dietary treatment are shown in table 2.

TABLE 2

Patient	Day attacks		Night attacks		Other symptoms	
	before	after	before	after	before	after
1	None	None	Frequent	None	Sneezing	None
2	Occas.	None	Frequent	None	Sneezing, lacrimation	Lacrimation unrelieved
3	Occas.	None	Frequent	Occas.	Sneezing	None
4	None	None	Frequent	Rare	Sneezing, lacrimation	Lacrimation partially relieved
5	Occas.	None	Frequent	None	None	None
6	None	None	Occas.	None	None	None
7	Occas.	None	Occas.	None	Sneezing, lacrimation	Both partially relieved
8	None	None	Rare	None	None	None
9	Rare	None	Rare	None	None	None

[1] The Harris diet is as follows.

On arising: 4 oz. of orange juice.

Breakfast: 1 fruit with or without cream—no sugar; 1 portion of cereal with 4 ounces of cream—no sugar; 1 egg; 2 or 3 slices of bacon, if desired; 1 slice of bread or toast with butter; Postum, caffeine-free coffee or very weak tea, no sugar.

2 hours after breakfast: 2 oz. of orange juice or 4 oz. of tomato juice.

3 hours after breakfast: 1 glass of milk.

Dinner: soup—cold or jellied chicken or beef consommé or tomato juice; 1 portion (100 gm.) of 5% vegetables; 1 portion (100 gm.) of 10% vegetables; 1 large portion of meat, poultry or fish; 1 slice of bread or toast; fruit with cream.

3 hours after dinner: 1 glass of milk.

1 hour before supper: 3 oz. of orange juice or 4 oz. of tomato juice.

Lunch or supper: 1 meat substitute—egg, fish or cheese; 1 salad—large serving of lettuce, cole slaw, tomato or Waldorf salad with mayonnaise or French dressing; 1 portion of 5% vegetables; 1 slice of bread with plenty of butter; fruit.

2 or 3 hours after supper: 1 glass of milk.

Every 2 hours until bed time: 4 oz. of orange or tomato juice.

Patients *10* and *11* were completely relieved of attacks. Patient *10* had been in the habit of taking injections of adrenalin about once a week. This was no longer necessary. Patient *12* had had chronic bronchitis with attacks of asthma requiring adrenalin once each night (about 2–4 A.M.) for a few years. He found that he could go for several days without adrenalin. There was no effect, of course, on the underlying bronchitis.

During the first 2 weeks of the dietary treatment, the patients noticed that they sometimes awakened with a sense of discomfort. Taking a little food soon made them comfortable enough to fall asleep again. Several patients (*cases 1*, 3, 4, 5 and 9) sometimes felt slightly uncomfortable (they wheezed a little) when they awoke in the morning. This was relieved immediately after breakfast.

The seasonal patients remained on the diet throughout the season of their sensitivity. At that time they were permitted to eat but 3 meals a day and were advised to avoid caffeine beverages and sweets. The chronic cases were advised to continue the diet indefinitely.

During the winter of 1939–1940, four of the first group of patients were again given a glucose tolerance test. The results, in mg. per 100 cc. of blood (table 3), show that the hyperinsulinism had disappeared.

TABLE 3

Patient	Fasting	Hours after ingestion of glucose					
		1	2	3	4	5	6
1	82	134	88	86	82	87	78
4	90	138	89	89	94	85	80
6	118	142	125	116	112	112	93
9	106	129	110	108	106	100	100

These same patients who had followed instructions, and 3 others who had disregarded all dietary advice after the end of their hay fever seasons, were seen during the summer of 1940. The 4 patients had no asthma but the other 3 again had asthmatic attacks. The glucose tolerance tests are given in table 4.

TABLE 4

Patient	Fasting	Hours after ingesting 100 gm. of glucose					
		1	2	3	4	5	6
1	75	132	82	80	76	78	78
4	92	142	95	90	86	86	84
6	94	140	98	87	90	86	87
9	76	118	86	88	88	88	89
2	88	138	100	82	80	68	59*
3	100	142	106	80	76	66*	
5	122	146	128	102	82	69	55*

* Asthmatic attacks

Six patients were studied during the summer of 1940. All had seasonal asthma. The procedure was simplified. Each patient was given 200 cc. of 50% glucose with instructions to finish his evening meal by 6 P.M. and to take no other food until the completion of the test. He set his alarm clock to awaken him at 4 A.M., when he drank the solution and went back to sleep. A fasting blood sugar determination was made at 10 A.M. Under these circumstances, a blood sugar concentration below 70 mg. per 100 cc. indicates hyperinsulinism (19). The results were as follows: *case 13*, 68; *14*, 66; *15*, 66; *16*, 54; *17*, 57; *18*, 62 mg. glucose per 100 cc. *Case 17* was wheezing slightly when the test was made. *Case 16* was so uncomfortable that the sample was taken at about 8:30 A.M. These patients were placed on the diet with uniformly good results.

DISCUSSION

The gratifying response to the dietary treatment is further evidence that hyperinsulinism plays a role in the development of asthmatic attacks. Allergy is too complex a phenomenon for us to say that hyperinsulinism is its cause. However, sufficient evidence has been brought forth to support the contention that, given the allergic sensitivity, hyperinsulinism brings about the hypoglycemia that permits the development of asthmatic symptoms. It may be that the allergic sensitivity produces hyperinsulinism. However, no matter what the exact mechanism involved in the production of seizures, they can be averted by treatment directed against the hyperinsulinism, alone. It may be said that hyperinsulinism is a necessary but not sufficient condition for the appearance of asthmatic attacks. That it is necessary can be seen from the uniformly positive results with the glucose tolerance test. The fact that hyperinsulinism can occur without any allergic symptoms demonstrates the truth of the latter half of the statement.

It has long been known that asthmatics have reason to dread the night for "the beginning is said to be most frequent during the night, when the patient has had his first sleep; for instance, at two or three in the morning he suddenly awakes with a stuffy feeling in his chest, and within a short time he is in the throes of an attack of asthma" (20). Now, there is no reason to assume that pollens are more concentrated in night air. Yet, these nocturnal episodes are not fortuitous, the blood sugar in patients with hyperinsulinism reaches its minimal value at precisely those hours. During the day, the meals are usually frequent enough to prevent a fall in blood sugar. Since the last meal is generally taken at about 6 or 7 P.M., there is ample time during the night for the blood sugar to drop below the physiological minimum.

We should expect, a priori, that the intravenous administration of glucose would be of benefit in treating asthmatics. This therapy has, indeed, been

recommended (21, 22, 23). It has never attained popularity because it soon becomes ineffectual. The concept of hyperinsulinism furnishes the only adequate explanation for this failure. The rapid increase in blood sugar following the injection stimulates the pancreas to secrete insulin. Then the over generous elaboration of the hormone causes the blood sugar to fall below the initial value. The net result, therefore, of administering glucose is to depress the blood glucose level.

Oral administration of glucose will likewise produce a temporary amelioration. This treatment has been used by Prince (24). However, the continued administration of glucose aggravates the condition and sugar has to be administered with increasing frequency. Another objection to the treatment is that it cannot be discontinued even for a few days.

Harris (16) also emphasized the effect of overindulgence in caffeine containing beverages. Caffeine, which is the only alkaloidal drug that is a common article of daily consumption, elevates the blood glucose (18), probably by stimulation of the adrenals. A rapid glycogenolysis takes place with consequent increase of the blood sugar concentration. The effect is the same, as far as the blood is concerned, as that following the actual ingestion of sugar or other carbohydrate. Many of the patients in the cases here reported were fairly heavy coffee drinkers. *Patient 1* had never drunk any coffee at all until 3 years ago when he acquired a taste for it and consumed several cups a day. His first allergic symptoms appeared in the summer of 1938. The attacks were mild and he maintained comfort throughout his hay fever season by taking an occasional capsule of ephedrin and amytal. He was sensitive to the early pollenating grasses, Timothy and June grass, giving positive skin reactions with both pollens. His symptoms, at that time, were not severe enough to warrant desensitization. During the summer of 1939, the attacks of asthma were sever and occurred almost nightly. They yielded completely to the dietary treatment. Under instruction, he drank two bottles of a popular caffeine containing soft drink and had a severe paroxysm a few hours later. The blood sugar, during the height of the attacks was 64 mg. per 100 cc. He was given some milk and the attack soon passed. This attack was induced, no doubt, by the large amounts of caffeine and sugar in the beverage. Except for this deliberate lapse, he followed the diet religiously for the remainder of his hay fever season. As was mentioned above, he dropped the diet in the fall but discarded coffee and excessive amounts of sweets. He has not been troubled since. *Patient 2* had symptoms for the first time during the summer of 1939. She had been very obese and, in an effort to lose weight, she followed a self-imposed diet which consisted, in the main, of drinking black coffee when the pangs of hunger became too severe. She admitted a consumption of 12 cups a day. She lost some 60 lb. in the effort and simultaneously acquired asthmatic attacks.

Harris found that patients with hyperinsulinism frequently have left upper quadrant tenderness. This was noted in 10 of the patients studied.

Peskin and Fineman (25) recommended a low carbohydrate, ketogenic diet for the relief and prevention of asthmatic attacks in children. Their diet is similar to Harris's except for the frequency of feeding and the effectiveness of such a regime can now be seen to be due to the depression of insulin production. *Patient 7* was a boy of 12 who had a history of epileptiform attacks for 3 years. He had been treated with a ketogenic diet. During 1937, he was given large amounts of glucose. That summer he developed hay fever. After the glucose tolerance test, in 1939, he was given the Harris diet. His attacks of unconsciousness were not controlled and further investigation demonstrated that he had true epilepsy. However, he went through 2 hay fever seasons without an attack of asthma.

It seems more than coincidental that the drugs commonly used for the relief of asthmatic attacks, such as morphine (26), amytal (27), ephedrin (28), and adrenalin (29) all raise the blood sugar. Caffeine also has this effect and it is occasionally used for acute attacks.

SUMMARY

A reciprocal relation between bronchial asthma and diabetes mellitus is suggested. Asthmatic attacks occur with a tendency to hypoglycemia. Asthmatics are made worse by sodium chloride, diabetics better. Asthmatics are prone to hypothyroidism and are relieved if they develop hyperthyroidism; the reverse is true for diabetics. The two diseases, although commonly occurring among the members of the same family, seldom occur in the same person at the same time.

It was assumed that bronchial asthma is associated with hyperinsulinism. This assumption was tested by performing 6-hour glucose tolerance tests on a number of asthmatics. There was a complete correspondence between the two conditions. The response to the treatment for hyperinsulinism justifies the claim that hyperinsulinism is one of the conditions necessary for the appearance of asthmatic attacks. However, not all persons with hyperinsulinism have asthma. The concept of hyperinsulinism furnishes the only logical explanation for the frequency of nocturnal asthmatic attacks. It also explains the failure of glucose to effect a lasting remission.

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PERCUTANEOUS USE OF TESTOSTERONE

INHIBITION OF LACTATION

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THE INHIBITION of lactation in women during the puerperium is almost always a painful process. Only an occasional patient goes through it without any discomfort. The largest number complain of soreness, heaviness, lumpiness and pain in the breasts. This often necessitates the continuous use of sedatives. A rise in temperature, malaise and general discomfort are not uncommon. These symptoms last from 3 to 7 days. The usual treatment instituted to dry up the breasts consists of limitation of fluids, tight breast binder, continuous ice caps to the breasts, saline cathartics, and sedatives.

The limited effectiveness and discomfort of these measures can be attested to by both patient and physician. In addition, the usual therapy adds considerable work to the nursing staff, especially when the patient is bedridden.

Interruption of the hormone balance with the object of inhibiting lactation, postpartum, has been attempted repeatedly. The barriers are our incomplete knowledge and inability to produce a pure hormone which will effectively induce this inhibition. Synthetic estrogen and androgen compounds have more recently been tried, in animal research and clinically. The impression has been gained that the effects are due to inhibition of the hypophysis when testosterone propionate was administered to animals and to man (1, 2).

Inhibition of lactation in the human being by means of testosterone propionate, was first reported by Kurzrok and O'Connell (3). 'Drying-up' of the secreting breasts was effectively accomplished without special nursing care, and with little or no discomfort to the parturient.

Bates et al. (4) have observed pronounced antigonadal effects in birds treated with related sex hormone preparations. Thus the effects of treatment with testosterone and related compounds were similar to those obtained by hypophysectomy. Rapid and extensive atrophy of the gonads and suppression of the follicle stimulating hormone followed. Mazer and Mazer (5) noted temporary but marked ovarian atrophy and consequent utero-vaginal effects, suppression of estrus, decrease in size of adrenals in the mature rat, and decrease in size of the pituitary in the immature rat, following prolonged treatment with testosterone propionate. Restitution of structure and function returned after this treatment was discontinued. Numerous reports (6, 7) have been published of suppression of menses following administration of male sex hormone in cases of menometrorrhagia and chronic cystic mastitis. Papanicolaou et al. (9) have shown decided change in the vaginal smear cytology, comparable with a low estrin phase, in these treated cases.

Suppression of gonadotropic properties in the human being by synthetic androgens has been reported by Hamilton and Wolfe (8). The increase of gonadotropic hormone subsequent to castration and in the menopause is in a great measure offset by injections of testosterone propionate.

Hamilton (8, 9) has reported histological changes in the hypophysis as well as suppressing and inhibiting effects when synthetic sterols and related compounds were administered to animals and in man. Structural changes in the pituitary have been noted following treatment with estrogens. These changes consist of degranulation of many or all of the basophils and to a lesser extent of eosinophils, with a concomitant increase of the chromophobes and a reduction in the percentage of the chromophils. Androgens produce only degranulation of the basophils.

One hundred consecutive cases from the obstetric services of the Bronx Hospital were treated with testosterone propionate. This was administered by inunction (4 mg. neo-hombreol dosules, Roche-Organon) in order to bring about suppression of lactation. Two dosules were given daily beginning with the second postpartum day. Each dosule was applied percutaneously to alternating areas such as the deltoid or the anterior surface of the thigh, etc. No other additional therapy was instituted.

A questionnaire was attached to the chart of each case and the attending physician answered all questions as to subjective and objective signs and symptoms as indicated.

The 100 cases reported were divided among 14 physicians, consisting of general practitioners, obstetricians and gynecologists.

RESULTS

The ages of the 100 parturient women were between 19 and 36; 60 were primipara, 40 multiparas. Reasons for 'drying-up' of the breasts were as follows:

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A. Maternal=77 cases.	
Anatomical malformations or inflammation of nipples	9
Economic or social reasons	34
Toxemia	2
Poor quality of milk	5[1]
Previous breast abscess	3
Previous feeding difficulty	10
Reasons not given	14
B. Fetal=23 cases	
Stillbirths	15
Neonatal deaths	7
Prematurity	1

[1] 3 cases were started on 5th day and 2 cases on 6th day.

The effectiveness of the therapy was judged by an interruption of the subjective symptoms and objective findings in the patients who were submitted to the medication. The results were grouped as follows: (*a*), optimum results, when inhibition of lactation was indicated by the absence of engorgement, distension, pain or discomfort, 68 cases; (*b*), partial result, when the above was accompanied by some engorgement and/or pain lasting from 4 to 40 hours, 29 cases and (*c*), failure, when no appreciable influence upon the breasts or subjective symptoms were noted, 3 cases.

In all cases during the puerperium one was able to express some milk from the breasts in both the optimum and partial result groups. This would indicate that the effect of the therapy was a diminution in the quantitative potency of the 'prolactin' rather than in the complete suppression of this pituitary principle. Of course further investigation and evidence is needed to establish this hypothesis.

There were no unpleasant by-effects resulting from the treatment. The normal character of the lochia was not changed. No after-pains were produced. In the successful cases, lactation, engorgement and pain in the breasts did not recur after treatment was stopped.

SUMMARY

Male sex hormone by inunction was effective in 68% of cases in whom for one reason or another inhibition of lactation was desirable. It was only partially effective in 29% of the cases. It was entirely without effect in 3% of the cases. In no case was lactation entirely arrested. The effect was rather a diminution in the degree of lactation with resulting diminution of secondary signs and symptoms, such as engorgement and pain. Testosterone, percutaneously, can successfully be used for the inhibition of lactation.

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STILBESTROL

USE OF STILBESTROL IN THE SUPPRESSION OF LACTATION

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SUPPRESSION of lactation is generally considered to to be a rather unpleasant ordeal. The indication for the elimination of this function may be an inability to nurse the infant because of a faulty nursing mechanism, the lack of need for nursing due to a stillborn child, an insufficient amount of breast milk, chronic disease, or a lack of cooperation on the part of the mother.

In any instance, the 'drying-up' process is usually painful, annoying and occasionally prolonged or difficult. The number of treatments recommended to accomplish this end are myriad. Breast binders, ice-bags, catharsis, limitation of fluids, massage with oils, injections of camphor preparations, breast pumps and other means have been offered as aids to the process of suppressing the production and flow of milk. The senior author aided in the development of a breast binder which proved to be highly efficacious (1).

In 1938, Dodds (2) introduced a new synthetic drug, diethylstilbestrol, which he showed had definite estrogenic properties and could be substituted for natural estrogens. In addition, stilbestrol, as it is known in the American literature, was found to be as effective by the oral route as by the parenteral route and some three to five times more potent than the natural hormone. Reports of various toxic reactions have limited its use but to date no permanent toxic results have been proven. Nausea and vomiting have been the most frequent manifestations of toxicity with occasional dizziness and skin rashes as other signs and symptoms. These toxic reactions have frequently been minimized by the use of smaller doses of stilbestrol.

The use of estrogenic hormones to suppress lactation is not a recent addition to the obstetrical armamentarium. We have used stilbestrol in more than 150 cases with varied indications for estrogens. In this series are 50 patients treated with stilbestrol for suppression of lactation. Recent articles concerning the use of stilbestrol for this purpose include those by Foss and Phillips (3), Winterton and McGregor (4), Kellar and Sutherland (5), Muckle (6) and Connolly, et al. (7). These authors describe various dosage of stilbestrol administered orally and intramuscularly. Uniformly, stilbestrol is noted to be an "efficient and safe method of suppressing lactation early in the puerperium (6)."

Early in our series, an effort was made to administer the drug only after we had a reasonable belief that the particular patient to be treated was going to have tender engorged breasts. Thus when lactation was to be suppressed because of poor nipples, a stillborn child, or any indication precluding any attempt at nursing efforts, stilbestrol was administered only after the breasts had begun to fill and the patient was becoming uncomfortable. When the mother had been nursing the child insufficiently, the drug was given when breast feeding was discontinued. No constrictive binders or other mechanical means were employed. Cathartics were not administered and fluids by mouth were not limited.

Five milligrams of stilbestrol in oil was injected intramuscularly at one time and usually only once. Later larger dosage was given as noted below.

DISCUSSION

Forty women were treated early in the puerperium before the tenth day. Thirty obtained relief within 6 to 16 hours which is certainly a more prompt response than we are accustomed to note with current methods of suppression of lactation.

Ten patients were treated late in the puerperium, between two weeks and two months after delivery, because of a diminishing milk supply. In all of these patients, lactation had been well established. Four patients responded very well with complete relief of pain and engorgment within 6 hours. The other 6 responded poorly, more poorly than we would expect from use of a constructive elastic breast binder.

Two patients were nauseated after intramuscular injections of 5 mg. of stilbestrol.

Recently two patients were observed after their second pregnancies. Each had had an abundance of breast milk with their first child and had also experienced great discomfort when their babies were transferred to artificial feedings late in the puerperium. For reasons unimportant to this discussion, breast feedings were to be foregone with the second preg-

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nancy. In each instance, 5 mg. stilbestrol was given intramuscularly on the morning of the second and third days postpartum. The breasts showed a short transient period of fullness and tenderness, not uncomfortable to the patient. Tight constrictive binders were not employed. Limitation of fluids was not advised. The results in both these cases were even more satisfactory than when the breast was allowed to begin to fill.

Since these experiences, our routine procedure with such patients who are not to be allowed to nurse the infant at all is to administer 5 mg. of stilbestrol on the morning of the first, second and third days postpartum; or to give 5 mg. on the second and third days; or 10 mg. on the second day only. Any one of these procedures seemed to be as satisfactory as any other one provided lactation had not made its appearance. The breasts remained soft and discomfort was noted by its absence.

When the dosage was increased to 10 mg. for suppression of lactation in those patients who had begun to nurse but had to be dried up, the results were possibly a bit more complete in respect to rapidity of relief of discomfort, but not markedly so. The greater dose was tolerated as well as the lesser one.

It was not an unusual occurrence to note recurrence of lactation about one week after cessation of treatment. Aside from slight annoyance, there was no pain or engorgment.

When lactation was adequate and stilbestrol was administered in treatment of threatened acute mastitis, nursing was continued without notable change in amount or character but with prompt alleviation of signs and symptoms of acute inflammation.

SUMMARY

A series of 50 patients treated with stilbestrol to suppress lactation is reported.

Five milligrams of stilbestrol was administered intramuscularly once, twice or three times.

Breast engorgment was relieved or inhibited within 16 hours in 30 of 40 patients in the early puerperium. Treatment after the second week of the puerperium, after lactation had been well established, did not prove to be so satisfactory.

Only two patients showed any reaction to the drug.

Stilbestrol is an excellent means of suppressing lactation in the early puerperium.

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STILBESTROL

TREATMENT OF THE MENOPAUSE WITH STILBESTROL

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SINCE DODDS (1, 2) first reported the estrogenic effects of stilbestrol there have been numerous reports of clinical trials with this interesting drug. Bishop (3) reported that in 17 of 25 women it controlled the symptoms of the menopause. He administered stilbestrol to a total of 46 patients of all types, only 3 of whom developed nausea and vomiting. A breast biopsy, made on one patient after she had received 280 mg. of stilbestrol, showed increased epithelial activity but no evidence of carcinoma. Winterton and MacGregor (4) observed nausea in 6 of 51 patients treated for amenorrhea, dysmenorrhea or the menopause. In 5 this symptom was slight and in one, severe enough to require omission of the drug. No other toxic reactions were noted. Others have reported similar results (5–14). Moricard and Saulnier (15), on the other hand, reported nausea in 7 of 12 patients. In 3 it was severe enough to make omission of the drug necessary. General malaise, nausea, vomiting and dizziness occurred in a large percentage of Varangot's (16) patients, leading him to question the value of stilbestrol. Loeser (17, 18) demonstrated fatty degeneration and necrosis of liver cells after administration of 1 mg. of stilbestrol daily to rats for 44 or more days. Shorr, Robinson and Papanicolaou (19) observed toxic reactions in 80% of 44 women given stilbestrol in doses adequate to control the menopause or produce estrogenic changes in primary amenorrhea. Liver function tests were inconclusive but suggested some functional impairment after these patients had been treated with stilbestrol. However, Buxton and Engle (20) reported no definite evidence of liver damage and only a small percentage of their patients developed nausea. MacBryde's experience with liver function tests (7) is similar. The consensus of most investigators seems to be that stilbestrol in therapeutic doses does not appear to be toxic, that nausea frequently occurs but is not sufficiently severe to warrant omission of the drug except in a small number of cases.

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During the last 16 months we have been using stilbestrol[1] in the treatment of the menopause. The patients were selected from the usual run of patients at the Central Free Dispensary. Only patients who appeared intelligent enough to evaluate subjective symptoms were selected. Each patient was observed for at least one month without medication, during which time she recorded the time and frequency of hot flashes and other symptoms of the menopause. Three vaginal smears were examined during the preliminary period and the vaginal smears were followed throughout treatment. There were 30 patients in this series, all of whom had symptoms characteristic of the menopause. Ten of these patients developed symptoms following pelvic surgery and the remaining 20 developed symptoms spontaneously.

RESULTS

All patients obtained prompt relief of symptoms of the menopause and showed characteristic estrogenic effects. Administration of the drug was followed by a decrease in hot flashes, nervousness, irritability, headache, dizziness and gastric and cardiac consciousness and an increase in vigor, appetite, libido and firmness and size of the breasts. There was an increase in the pigmentation of the nipples in most instances and in several instances, in that of the genitalia. When senile vaginitis was present, it disappeared promptly. The minimum effective dose was usually about 2 mg. daily, although as little as 0.5 mg. per day completely controlled symptoms of the menopause in one patient and as much as 6 mg. daily was inadequate for complete control in another. Vaginal bleeding occurred frequently during the administration of the drug in patients previously presenting amenorrhea and, on omission of the drug, in all patients who had an intact uterus, irrespective of age. The results are given in detail in table 1.

[1] The stilbestrol was supplied by Dr. J. A. Morrell of E. R. Squibb & Sons and by Dr. R. M. Johnson of Frederick Stearns & Co.

TABLE 1. RESULTS OF TREATMENT

Case	Age	Diagnosis	Months treated	Daily dose	Total dose	Daily dose required to control symptoms	Bleeding during treatment	Bleeding on stopping stilbestrol	Vaginal smear before stilbestrol	Daily dose required to convert vaginal smear to interval type	Untoward symptoms	Remarks
				mg.	mg.	mg.				mg.		
1	38	AM	4	2–3	284	2	–	–	m	3	None	Panhysterectomy
2	37	M	8	2–6	526	?	+	+	m	5	Nausea, vomiting, diarrhea when dose of 5 mg. daily first given. Tolerated 3 mg. well. Later no intolerance to 6 mg. daily. Severe uterine hemorrhage.	Bilateral cystic ovaries removed during treatment.
3	32	AM	3	1–3	202	3	–	–	I		None	
4	32	AM	½	1	14	?	–	–	I		Refused to continue treatment because of nausea.	Hysterectomy
5	47	M	12	0.1–3	545	3	–	–	m	1	None	Hysterectomy
6	39	AM	4	0.3–3	75	3	–	–	I		None	Panhysterectomy
7	39	AM	4	1–3	196	3	–	–	I		Slight nausea first week of treatment	Panhysterectomy
8	47	M	3	1	64	?	–	+	m	?	Nausea and vomiting first 2 wk.	Thyroidectomy requiring omission of treatment
9	50	M	3	1–2	144	2	–	+	m	1	Thrombophlebitis	
10	45	M	10	0.3–3	237	3	+	+	m	3	Severe uterine hemorrhage requiring transfusions	
11	47	M	10	0.4–3	358	2	+	+	m	2	Severe uterine hemorrhage	Fibroids of the uterus
12	42	AM	8	0.3–1	91	0.5	–	–	m	1	None	Panhysterectomy
13	48	M	15	0.3–3	703	2	+	+	m	1	Slight nausea during first month of treatment	
14	43	M	9	0.3–2	163	2	+	+	I		Severe uterine hemorrhage	
15	62	M	15	1–3	714	2	+	+	m	1	Slight nausea and occasional vomiting first week	
16	51	M	14	0.3–2	292	1	+	+	m	1	Slight nausea for first week of medication	
17	43	M	8	0.3–2	189	2	+	+	m	1	Slight nausea for first 2 wk.	
18	41	M	11	0.3–3	680	3	+	+	m	3	Slight nausea first week	
19	49	M	4	0.5–1	89	1	+	+	m	1	None	
20	46	M	8	1–2	224	2	–	+	m	1	None	
21	49	N	9	0.5–3	416	2	–	+	m	1	Nausea, vomiting, and diarrhea while taking 3 mg. daily but not 2 mg. daily	
22	56	M	12	0.1–3	332	2	+	+	m	1	None	
23	50	M	9	0.3–3	219	3	+	+	m	3	Abdominal cramps first week of treatment	
24	32	AM	10	0.2–3	434	3	–	–	I		Slight nausea and one emesis first week	
25	53	M	3	1	117	1	+	+			Died; cerebral embolus, hepatitis	Hypertensive heart disease
26	57	M	2	0.3–1	38	1	–	?	m	0.3	None	Drug has not been omitted.
27	44	AM	3	0.3–1	43	1	–	–	m	0.3	Slight nausea first week	Panhysterectomy
28	49	M	2	0.1–2	18	2	+	+	m	2	None	
29	33	AM	1	0.3–1	40	1	–	–	m	0.3	None	Panhysterectomy
30	34	AM	3	0.3–2	102	2	–	–	m	2	Nausea first week	Hysterectomy

AM—Artificial menopause
M—Physiologic menopause

m—Menopausal vaginal smear
I—Interval vaginal smear

UNTOWARD REACTIONS

No changes have occurred in the urine of any patients and the blood counts, when obtained, have been normal with the exception of 2 patients who developed a temporary anemia following uterine hemorrhages. Most of the patients experienced slight nausea and occasionally vomiting, when the drug was first started. These symptoms were less frequent when the drug was given just after a meal. Enteric coating of the tablets apparently did not prevent nausea. Nausea disappeared within two weeks in most cases if the drug was continued. Two patients

who tolerated well a dose of 2 mg. daily experienced troublesome nausea when the drug was increased to 3 mg. daily. Several patients experienced slight nausea on restarting the drug after a period of omission but this symptom disappeared after a few days. Nausea, vomiting and diarrhea were so severe in one patient that omission of the drug was necessary.

Uterine hemorrhage became sufficiently severe in 4 patients to require omission of stilbestrol temporarily. One of these patients had uterine fibroids and had menstruated profusely before the onset of the menopause. Bleeding was severe enough to require hospitalization in 2 patients. One was a 45-year-old woman who had had a radical breast amputation 18 months previously. She had been bleeding slightly from the uterus for two months while taking 3 mg. of stilbestrol daily and when it was omitted a severe hemorrhage developed. She was admitted to the Cook County Hospital without our knowledge, where a diagnosis of bleeding fibroids was made, the attending physician apparently not having any knowledge of her previous medication. Two transfusions of 500 cc. of whole blood were given, following which an exploratory laparotomy was done, which revealed no abnormality in the pelvis. A curettage was made and the endometrium was reported to show a "resting stage with cystic hyperplasia." She has been on stilbesterol for 4 months since discharge from the hospital and has had no futher severe bleeding, although slight bleeding has occurred on omission of the drug. The other patient was a 37-year-old woman who had had two normal pregnancies. At the age of 35 years she developed scanty menstrual periods and severe symptoms of the menopause. At the age of 36 years she had been told by a physician that she had cystic ovaries. After receiving from 3 to 5 mg. of stilbestrol daily for 3 months with partial relief of her symptoms, she began to bleed profusely. After omission of stilbestrol a severe uterine hemorrhage occurred and it was considered advisable for her to enter the hospital. The bleeding stopped 10 days after omission of the drug. Two weeks later she was readmitted to the hospital with a diagnosis of twisted ovarian cyst. At operation both ovaries showed extensive cystic changes and the right ovary was twisted on its pedicle. The endometrium was hyperplastic.

One patient developed an extensive thrombophlebitis of a varicose vein in her leg while taking stilbestrol. This gradually subsided on omission of the drug and did not recur when the drug was administered later.

One possible danger of the drug may be the development of thrombocytopenia, as demonstrated by MacBryde (7) and Tislowitz (21). Unfortunately, platelet counts were not made during the period of hemorrhage in our 4 patients who developed severe bleeding from the uterus. At present the platelet counts on these patients are normal.

We have not observed any definite decrease in effectiveness of stilbestrol with prolonged administration although we have had one patient taking the drug continuously for 16 months, except for a period of omission of 5 days duration every 6 weeks.

Although we have had untoward reactions as far as bleeding is concerned, we now feel that the danger of bleeding can be reduced by withdrawing the drug as soon as bleeding appears or by periodic omission of the drug. This is usually followed by a moderate flow but not by severe hemorrhage.

There is some question as to what effect any of the estrogens may have on the ovaries. As reported above, cystic ovaries were found at operation in one of our patients who had been taking large doses of stilbestrol for a period of about 4 months. However, this patient had had symptoms of hypoövarianism for 2 years before treatment with stilbestrol. This suggests that ovarian pathology was probably present before treatment was started.

The possible role of stilbestrol in causing liver damage has been brought to our attention by the pathologic findings in a 53-year-old woman with arteriosclerotic heart disease and hypertension who developed slight jaundice and died suddenly. She had had a total of about 131 mg. of stilbestrol in doses of 1 mg. daily over a period of 5½ months before the development of jaundice. This patient had been seen frequently by us for 6 years because of parathyroid tetany following a thyroidectomy for exophthalmic goiter at the age of 47 years. She had received 400,000 U of theelin in 1938, which had partially controlled her menopausal symptoms. During the 6 years of observation there had been an increasing hypertension and changes in the retinal arteries. Stilbestrol was first administered from March 13, 1940 to July 8, 1940 with complete relief of menopausal symptoms and without any toxic reaction. On August 8, 1940, she returned to the clinic complaining of a recurrence of headache, weakness and dizziness, which had been relieved previously while taking stilbestrol, and in addition a loss of 10 lb. associated with anorexia and nausea. Stilbestrol in a dose of 1 mg. daily was restarted. This controlled her headache but the nausea and anorexia continued. She became too weak to come to the clinic and was admitted to the hospital August 23, 1940. She appeared slightly jaundiced and had lost another 10 lb. She had had no stilbestrol for one week and jaundice had been first noted by her daughter 3 days before admission to the hospital. She died suddenly during the first night in the hospital, apparently from a cerebral hemorrhage or embolus. Aside from the findings of left ventricular

hypertrophy, generalized arteriosclerosis especially of the coronary arteries, and changes in the glomerular tufts of the kidneys and focal areas of round cell infiltration in the parenchyma of the kidneys, the autopsy revealed nothing unusual except for the liver. The liver weighted 1570 gm. It appeared to be firmer than usual and the edge and surface were smooth. Multiple sections showed an unusual slate brown color with some yellowish mottling caused apparently by deposition of fat. The cut surface presented a pale icteric tint. The gross appearance was like that seen in cases of hepatitis. The gall bladder and ducts were grossly normal. Microscopic sections of the liver showed in many places vacuolization which appeared to be between the hepatic cells. However, vacuoles were seen in some of the liver cells. The hepatic cords were swollen. In many places the cells were indistinct in outline, assumed various shapes and showed granular cytoplasm. The nuclei of many of them, although centrally placed, were swollen. The sinusoids contained some red blood cells and in some of the Küpfer cells there was some iron containing pigment. The bile capillaries were unchanged. The central vein was partially filled with blood cells and the portal vein was dilated and also contained blood cells. Focal areas of round cells were seen in one of the sections in the region of the portal vein. Glisson's capsule was not thick but in some places beneath the capsule there were collections of round cells.

The hepatitis in this patient was apparently of recent origin because of the absence of cirrhosis. The problem was whether it was related to the hypertensive heart disease with kidney damage, the attack of exophthalmic goiter, recent starvation or stilbestrol. Liver changes not unlike those found in this patient have been described by Loeser (17, 18) following the administration of stilbestrol to rats. Since the first course of treatment with stilbestrol was not associated with any untoward symptoms and since for several years she had had symptoms referable to hypertensive heart disease and arteriosclerosis, it is possible that the terminal symptoms and liver changes were caused by these disorders and not by stilbestrol.

SUMMARY

Stilbestrol has been administered orally for periods of from 3 to 16 months to 25 patients suffering from the menopause. Nausea occurred frequently during the first few weeks of treatment but was troublesome enough to require omission of the drug in only one case. The maintenance dose was about 2 mg. daily in a large number of patients but varied from 0.5 mg. to more than 5 mg. daily. One patient with hypertensive heart disease died one week after omission of treatment and the liver showed evidence of toxic hepatitis similar to that found in test animals receiving stilbestrol. However, the changes in the liver of this patient may have been related to cardiorenal disease or starvation. Uterine bleeding became troublesome in 4 patients and dangerous in 2 of them. The danger of uterine hemorrhage may be reduced by periodic omission of the drug. But some bleeding commonly occurs in patients with intact uteri when the drug is withdrawn. One patient developed thrombophlebitis while taking stilbestrol and another required surgical intervention because of a twisted ovarian cyst. However, the history suggests that the ovaries had been cystic before the ingestion of stilbestrol.

CONCLUSIONS

Stilbestrol is a potent estrogenic substance which combines the advantage of being very effective by mouth with that of low cost. Most patients tolerate the drug well.

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STILBESTROL

EFFECT OF STILBESTROL ON THE MYOMETRIAL AND ENDOMETRIAL ACTIVITY OF THE HUMAN CASTRATE UTERUS

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IN THE PAST THREE YEARS many articles have been written about the synthetic estrogen, 4-4′ dihydroxy A B diethylstilbene which is now referred to as diethylstilbestrol or more simply stilbestrol, and which was discovered by Dodds and his coworkers (1). This estrogen, differing distinctly in chemical structure from the previously known estrogens, has been shown to produce all the biologic effects attributed to them, such as suppression of the antuitary (2), inhibition of body growth (2), proliferation of the ductile system of the breast (3), suppression of engorgement incident to lactation (4), hyperemia, edema, and distention of the uterus (5), proliferation of the endometrium (6), vaginal cornification (7), and swelling of the sexual skin (8). It likewise presumably has the supposed carcinogenic propensities of the true estrogens (9).

One of us (J.E.L.), in previous publications (10, 11), has demonstrated the effect of estrogenic substance on myometrial activity in the human uterus by utilization of the intrauterine bag. We felt that it might be of interest to apply this same method in a similar study using stilbestrol as the experimental agent. The subjects of our study were surgically castrated women, as we were desirous of avoiding a possible enhancing effect of endogenous estrogen such as could be elaborated in the normal sexually active female. It appears that post menopausal women secrete a small but definite quantity of estrogen possibly by way of the adrenals (12). Geist (12) states that the surgical castrate likewise probably produces endogenous estrogen. However, the abrupt cessation of ovarian activity coupled with clinical evidence of severe estrogenic deprivation in such patients, might lead one to deduce that the responsible glands do not have time to take over the function of the ovary and that these women may produce less estrogen than the post menopausal group and perhaps may produce none at all.

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Finally it was considered of value to correlate endometrial with myometrial activity (as evidenced by the endometrial biopsy) as a means of studying the relative rates at which these structures respond to the influence of stilbestrol.

This study was made on two castrate women. The first (*Mrs. A. S.*) was a 35-year-old married nulligravida who had had a bilateral salpingo-oöphorectomy for pelvic inflammatory disease at 18 years of age. Her weight was 285 lb. The uterus was hypoplastic. A control uterine tracing taken at the beginning of the experiment revealed a uterine volume of 1.0 cc. with no spontaneous motility at the end of 90 minutes (fig. 1). Endometrial biopsy obtained at the same time demonstrated an endometrium with no glandular tissue and scanty stroma (fig. 3). Thereafter for a period of 20 days, the subject was given 5 mg. of stilbestrol intramuscularly each day, obtaining uterine tracings and endometrial biopsies at 5-day intervals. After 25 mg. of stilbestrol had been administered, the uterine volume had increased to 2.4 cc. and the tracings of uterine motility showed small spontaneous contractions unaffected by pituitrin; there were no changes in the endometrium, contrary to the observations of Wenner and Joel who found endometrial proliferation following administration of 15 mg. of stilbestrol parenterally (4). No complaints, other than moderate nausea could be elicited from the patient. Five days later, following another 25 mg. of stilbestrol, uterine volume persisted at 2.4 cc.; tracings of uterine motility showed moderate contractions (fig. 2). At this time the endometrium had been converted into a characteristic proliferative phase (fig. 4). Nausea persisted, and the patient noted a marked libido for the first time in many years. After 100 mg. of stilbestrol had been administered, the myometrium had undergone no further change, although the uterine volume had shown a further increase to 3.1 cc.; the endometrium was now definitely hyperplastic (fig. 5). At this point stilbestrol injections

were stopped, and the subject given a hypodermic injection of 5 mg. of progesterone (proluton) daily for 10 days. Profuse vaginal bleeding appeared 2 days after the administration of stilbestrol was stopped, and persisted for a period of 12 days, unaffected by progesterone. The latter caused no change in myometrial activity, but the endometrium showed subnuclear vacuolization generally recognized as early secretory activity (fig. 6). Biopsy taken 6 weeks later showed an endometrium in the early proliferative phase.

the extent noted in the first case (fig. 8). Moderate vaginal bleeding began 5 days after the close of the experiment, and persisted for 8 days. No untoward symptoms due to stilbestrol could be elicited from the subject.

DISCUSSION

Unfortunately, we were able to study only two women, since the nature of the material and the experiment made it impossible to obtain any more patients. Correlated studies of the endometrial and

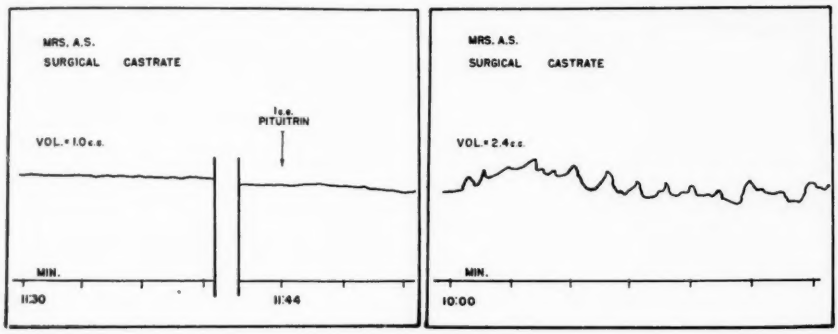

Fig. 1. (left) (*Case 1*). CONTROL UTERINE TRACING TAKEN AT START OF EXPERIMENT. No spontaneous motility. No response to pituitrin. Vol., 1.0 cc. Fig. 2. (right) (*Case 1*). UTERINE MOTILITY FOLLOWING ADMINISTRATION OF 50 MG. STILBESTROL. Vol., 2.4 cc. Moderate arhythmic contractions.

The second patient (*Miss R. S.*) was a 29-year-old unmarried nulligravida who had had a bilateral salpingo-oöphorectomy for ovarian dermoids at 14 years of age, two weeks after the onset of her first menstrual period. Her weight was 134 lb. Secondary sexual characteristics were well developed and the patient admitted an active libido. Her uterus was small and freely movable. Initial tracings showed no spontaneous motility, and no response to pituitrin (fig. 9). The volume of the uterus was 0.5 cc. The endometrium was in an atrophic state (fig. 7). Five mg. of stilbestrol were administered daily by mouth for a period of 14 days, at the end of which time, very small spontaneous contractions were obtained with the intrauterine bag. The uterus did not respond to pituitrin, and its volume was unchanged. Biopsy revealed a proliferating endometrium. Stilbestrol was continued orally for another 15 days for a total dosage of 145 mg. and tracings and biopsies were obtained at 5-day intervals. The myometrium continued to show some evidence of activity by contractions alternating between rhythmicity and arhythmicity but did not respond to pituitrin. Uterine volume, however, showed a rapid and notable increase to a peak of 2.7 cc. at the close of the experiment (fig. 10). The endometrium developed full estrogenic activity with occasional cystic dilatation of the glands not, however, to

myometrial activity in the human castrate have not previously been made, insofar as their time response to stilbestrol stimulation is concerned. In the first case, uterine motility and increased volume appeared at least several days before the endometrium showed any histological changes. If the uterine body reacts to estrogens by increased oxygen consumption (elevated metabolic rate) as shown by Reynolds (13), it would be reasonable to assume that both the myometrium and endometrium would respond simultaneously. Reynolds subsequently demonstrated (14) that stilbestrol does not have the cholinergic effect on the uterus (which precedes metabolic activation by several hours) that the true estrogens have. In the second case, motility and proliferation were concomitant, with increased uterine volume appearing later. In both cases, motility was not markedly stimulated, as evidenced by the small uterine contractions. The straight line of the control tracing taken in each case proves that the motility was not due simply to the presence of a foreign body within the corpus cavity.

The increased uterine volume is likewise of interest. It presumably is not analogous to the uterine distention of experimental animals in which the corpus cavity is filled with mucin. Changes in the endometrium correlate with observations made by other investigators (15) regarding the effect of stil-

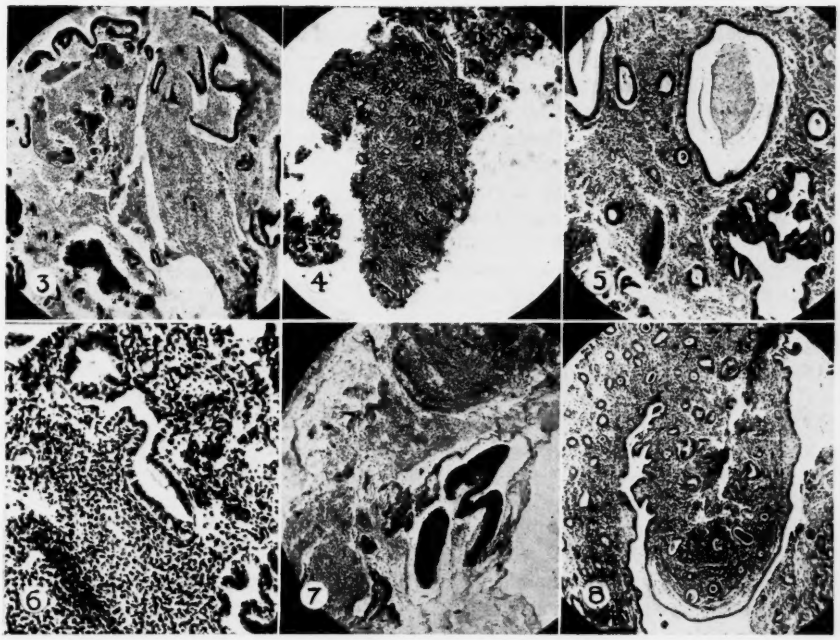

Fig. 3 (*Case 1*). ATROPHIC ENDOMETRIUM. Scanty stroma; few poorly developed glands. Biopsy obtained prior to therapy. ×30. Fig. 4 (*Case 1*). ENDOMETRIAL BIOPSY AFTER ADMINISTRATION OF 50 MG. STILBESTROL. Proliferative phase. ×30. Fig. 5 (*Case 1*). HYPERPLASTIC ENDOMETRIUM PRODUCED BY 100 MG. OF STILBESTROL. ×30. Fig. 6 (*Case 1*). ENDOMETRIUM AFTER 50 MG. PROGESTERONE. Subnuclear vacuolization present. Stroma still compact. ×90. Fig. 7 (*Case 2*). ENDOMETRIAL BIOPSY PRIOR TO THERAPY. Endometrium atrophic. ×30. Fig. 8 (*Case 2*). ENDOMETRIAL CHANGES INDUCED BY 145 MG. STILBESTROL. ×30.

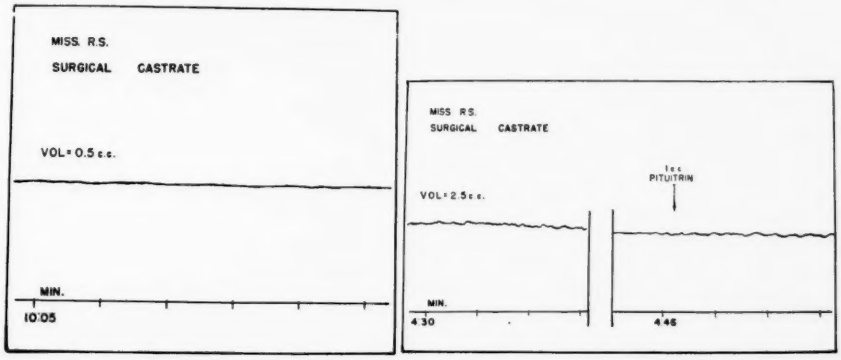

Fig. 9 (left) (*Case 2*). CONTROL UTERINE TRACING TAKEN AT START OF EXPERIMENT. Vol. of uterus, 0.5 cc. No spontaneous motility. Fig. 10 (right) (*Case 2*). UTERINE MOTILITY AFTER INGESTION OF 145 MG. OF STILBESTROL. Small arhythmic contractions. No response to pituitrin. Vol. of uterus, 2.5 cc.

bestrol on this tissue. There is no detectable histological difference between these changes and those observed by administration of the natural estrogens. In the first subject, a typical 'Swiss cheese' endometrium was obtained, having evolved from simple proliferation, and was responsible for severe bleeding upon estrogen withdrawal. In this same subject, 50 mg. of progesterone produced only subnuclear vacuolization in the endometrial glands (considered as early secretion). The glands showed no other evidence of morphologic change, and the stroma remained compact. Progesterone appeared to have no

effect on the estrinpriva bleeding. In the second subject, endometrial changes were not so prominent despite the increased amount of stilbestrol given, perhaps due to its mode of administration (oral). A few cystic glands were observed, but never a typical hyperplasia. Estrogen deprivation bleeding was neither so marked nor so long as in the first subject.

Clinically, the only untoward effect associated with the administration of stilbestrol in this study was a moderate nausea in the first patient persisting for the duration of the experiment. This same patient has developed a marked protracted libido. The second case manifested no demonstrable effects either untoward or advantageous.

SUMMARY

A study of the influence of stilbestrol on myometrial and endometrial activity has been undertaken in two surgically castrated women by utilization of the intrauterine bag and endometrial biopsy. In both women stilbestrol induced spontaneous uterine contractions and endometrial proliferation. In the first subject, motility of the uterus preceded proliferation of the endometrium by several days; in the second patient they were concomitant. Changes in the endometrium were more marked than in the myometrium, varying in degree, however, in each subject. These changes were only slightly influenced in the first case by subsequent administration of progesterone. Both patients developed estrinpriva bleeding as a result of stilbestrol withdrawal. This was more severe in the patient with typical hyperplasia induced by parenteral administration. One subject developed a persistent libido as a result of medication, including with moderate nausea, the only subjective effects of the drug.

We wish to thank the Schering Corporation and the Abbott Laboratories for the supplies of progesterone and stilbestrol used in this study.

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STILBESTROL

SUMMARY OF SOME CLINICAL REPORTS ON STILBESTROL

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DURING the comparatively short time since the discovery of stilbestrol by Dodds (1) and his associates to the present[1] the writer has abstracted 257 papers in which stilbestrol was either the entire subject or an important part thereof. Many of these have been reports from the laboratory confirming the similarity of physiological action of stilbestrol and the natural estrogens. Some few have discussed pharmacological and pathological studies which have been made with the substance. Many others have reported the results of the clinical application of stilbestrol in the various conditions in which the natural estrogens have been employed.

No review of the clinical work has been published so far and it was felt that such a summary might have a definite value at this time. No attempt has been made to present a complete tabulation of all the clinical papers that have appeared because many of these do not lend themselves to such treatment. Some mention stilbestrol in general terms as a substitute for the natural estrogens. Others simply state that stilbestrol has been employed in the treatment of several different types of estrogen deficiency with more or less success.

In table 1 are presented the data contained in 64 published papers: 50 American, 6 English and 8 from other countries.

DISCUSSION

The results indicate that there is no question about the estrogenic activity of stilbestrol. These reports show that it is as effective if not more so than the natural estrogens in any of the clinical conditions in which it has been tried. It is very active when given orally in contrast to the natural estrogens. Excretion studies (66) have shown that appreciable amounts of stilbestrol are excreted in the urine whereas much smaller amounts of the natural estrogens are found there. The metabolism of stilbestrol has not been extensively studied but the difference both in amounts and in duration of excretion may indicate a difference from the natural estrogens.

Stilbestrol is also very effective when given intravaginally, percutaneously or by subcutaneous implantation of pellets. In view of the cheapness of the product and its effectiveness by the oral route it would seem that the implantation method is not as important as it is in connection with the steroid hormones.

Stilbestrol has never been reported to occur in the animal body or its excreta. Hence it must be considered a drug rather than a hormone. Naturally a great deal of interest has been taken in the possible toxicity of the compound.

One manifestation of possible toxicity, nausea, has been a very common symptom displayed by patients taking stilbestrol. The incidence of this symptom varies enormously as can be readily seen from the table. It has been reported as ranging from occasional and transitory nausea to an incidence of 80% and of a severe and persistent character. It has been stated (56) that the nausea is central in origin but this has not been substantiated. Recently (29) an observation has appeared showing that probably small doses exert an irritating effect producing hyperacidity and large doses have a depressant effect which may account for the nausea. Experience has shown that the incidence of nausea is higher on large doses than on small ones and, further, that many individual patients can take 1 mg. or even 2 mg. with no nausea or other side effects but cannot take larger doses without nausea. A general trend towards reduction of the dosage employed can be observed as more experience is obtained.

Different routes of administration show also a difference in the incidence of nausea. In one recent report (24) it was shown that nausea occurred least frequently where stilbestrol was given hypodermically, and, in order of increasing frequency, percutaneously, intravaginally, and orally. There apparently are some patients who cannot tolerate the drug in any dosage or by any route of administration. However, this is a small percentage of the total, probably from 3 to 5%.

Many different palliative measures have been tried by various clinicians. These methods have included giving stilbestrol (*a*) always on a full stomach, (*b*) an hour before retiring, (*c*) as enteric coated tablets, (*d*)

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[1] Feb. 1, 1941.

TABLE 1. TABULATION OF 64 PUBLISHED PAPERS ON STILBESTROL (American 50, English, 6, Other countries 8)

Author and reference	Cases	Nausea	Vomiting	Other side reactions	Stopped treatment	Menopause, cases	Inhibition of lactation, cases
		%	%	%	%		
Allan (2)	45	22	6.6		4.4	45	
Abarbanel (3)	175						175
Bishop (4)	45	6.6	6.6			15	
Buschbeck (5)	90	Considerable proportion except on puerperal cases					
Burch (6)	16	No mention					
Buxton (7)	17	17.7	6			11	
Collins (8)	50	Transitory 60%	Severe 2%			35	
Connally (9)	200	No single toxic side effect					
Cohn (10)	25	No mention					
Davis (11)	102	5 mg. 20%	1 mg. 3%			100	
Evelbauer (12)	50	Well tolerated except in hypoplastic cases					
Everett (13)	32	12.5	1 mg. none			32	
Ewing (14)	15	No mention					
Farthing (15)	24	No untoward side reactions				20	
Felding (16)	55	16.3			14.5	45	
Felger (17)	74	Mild 14.8 Mod. 12.2 Severe 9.0	5.4	9.0		68	
Finkler (18)	4	No mention					
Frank (19)	42	12.0				42	
Franke (20)	80	No untoward effects				80	
Freed (21)	21					20	
Fuestner (22)	128	Mild 12.5	3.1			64	54
Geist (23)	38	Hypo 20 Oral 45		Some		38	
Greenblatt (24)	79	Hypo 11 Oral 50 Vaginal 26 Percutaneous 13					
Greenblatt (25)	22	13.6					
Heaver (26)	26	Some side reactions in 23%					
Huberman (27)	77	36.0		31		77	
Huett (28)	46	10			3		
von Haam (29)	125	35		20		125	
Jeffcoate (30)	11	No mention					
Kahle (31)	14	14.3		7			
Karnaky (32)	178	Occasional				60	
Karnaky (33)	100	Some					
Karnaky (34)	700					75	5
Karnaky (35)	128						
Keller (36)	19	Oral—temporary 16 Hypo— 0				6	4
Kurzrok (37)	40	Menopause 67 Others 50				15	
Lewis (38)	18	Menopause 20				10	
MacBryde (39)	56	16			3.6	51	
MacBryde (40)	14						
Moricard (41)	12	Some				12	
Muckle (42)	75	2.6 Sl.					75
Muckle (43)	133	2.8					133
Payne (44)	52	10				52	
Payne (45)	80	23.7		5	7.5		
Peel (46)	79	1.27					
Preissecker (47)	70	Some—adjust dosage. No nausea in pregnant or lactating women					
Pratt (48)	250	5.2			3.6	124	
Palmer (49)	8	No mention				4	
Palmer (50)	31	35					
Resnik (51)	11	18				4	1
Rosenkranz (52)	40	No toxicity—pregnant women					
Russ (53)	25	None with milk					
Salmon (54)	45	55		Some		45	
Sevringhaus (55)	17	5.9		5.9			
Short (56)	44	80	32	70		42	
Soule (57)	64	Some side reactions		17	14	31	7
Tietz (58)	120	No adverse effects in doses not exceeding 2.5 mg.					
Tietz (59)	51	5.9					
Weed (60)	57	No nausea with milk				57	
Weinstein (61)	100	15			1.1	86	

TABLE (*cont.*) TABULATION OF 64 PUBLISHED PAPERS ON STILBESTROL (American 50, English, 6, Other countries 8)

Senile vaginitis, cases	Amenorrhea, cases	Dysmenorrhea, cases	Hypoestrinism, cases	G.C. vaginitis, cases	Uterine bleeding, cases	Pregnancy & complications, cases	Mental cases	Miscellaneous	Liver function tests
10	18	2							
	16								
4	1		1						1 possible damage
2			13						
						200			
				25					
	2								No liver damage
	7							8	
								4	
			10						
4								2	
4									
								1	No liver damage
10									
							26		
									No liver damage
						11			
								14	
16	25	1	11	5	60				
26	24	24	37	17	400			91	
					7			121	
5	3					1			
	25								
				8					
	5								No liver damage
									No liver damage
									No sign of liver damage
									1 possible damage
						79			
67	3				7			27	
	4								
					31				Possible damage
	4	1						1	
						40			
				25					
	2								Inconclusive
5		5	11					6	
							51		

TABLE 1—*Continued*

Author and reference	Cases	Nausea	Vomiting	Other side reactions	Stopped treatment	Menopause, cases	Inhibition of lactation, cases
		%	%	%	%		
Werner (62)	29	6.9				9	20
White (63)	16						
Wilder (64)	66	Nausea controlled by milk of magnesia				50	1
Winterton (65)	51	12			1.9	30	6
Totals	4507					1580	481

with simultaneous administration of bile salts, (*e*) with bread, (*f*) powdered in milk, (*g*) with milk of magnesia. There does not seem to be any common denominator for these various attempts to obtain relief from nausea.

Vomiting as the objective symptom of gastrointestinal disturbance occurs much less frequently than nausea.

Other side reactions which have been reported following the use of stilbestrol, listed in approximate order of their frequency as reported in an additional series of 2,196 cases (67), are loss of appetite, abdominal distress, headache, diarrhea, drowsiness, vertigo, palpitation and skin eruptions.

Curiously enough during pregnancy and the puerperium side reactions are practically absent even in spite of enormous doses. White (63) has given a 40–120 mg. daily to pregnant diabetics exhibiting severe toxemias of late pregnancy and pre-eclamptic states with no side reactions and no evidence of damage to the liver.

Liver function studies (7, 11, 21, 29, 39, 40, 45, 50, 56, 63, 68) have not shown any clear-cut evidence of damage to this organ. In about 3 instances there was a possibility that liver injury might be attributed to stilbestrol, but secondary unrelated complications might also account for these.

Studies on blood morphology and constituents (7, 11, 29, 40, 45, 68) of patients receiving stilbestrol for varying periods of time and in widely divergent conditions and dosage have shown no change of pathological nature. In a few instances cases exhibiting varying degrees of anemia have shown a considerable increase in erythrocyte count and hemoglobin concentration.

Less work has been reported on studies of blood chemistry of patients treated with stilbestrol. However, at least three authors (7, 41, 68) have found no significant changes in the chemical components of the blood in patients under such treatment.

Reports (7, 11, 39, 40, 68) of findings from chemical studies of the urine of stilbestrol treated cases have shown nothing abnormal.

Apparently the administration of stilbestrol may result in nausea either temporary or persistent and severe of unknown cause and mechanism with a much smaller number of patients exhibiting a wide variety of occasional side reactions. However, definite evidence of any permanent toxicity is still lacking.

Another consideration, the side effects of excessive estrogen dosage, must be mentioned. Some authors have suggested that many of the so-called toxic side effects enumerated above might be due to estrogen overdosage rather than toxicity of stilbestrol. However, another group of side effects must be mentioned which are primarily related to the physiological estrogenic effects.

In menopausal cases, particularly those having various complications and in children with gonorrheal vulvovaginitis, uterine bleeding is a frequent occurrence. Excessive bleeding to the point where it becomes alarming or dangerous very seldom occurs. This withdrawal bleeding may occur while the patient is still continuing treatment as has been reported in cases treated with natural estrogens. However, bleeding occurs more frequently with stilbestrol than with the hormones and patients should be warned of the possibility and urged to return at once if the flow is abnormally profuse or prolonged. Otherwise the occurrence has little significance.

The breasts of patients treated with stilbestrol frequently increase in size or fullness sometimes even becoming sensitive to touch or painful and the nipples and areolae become pigmented. These changes are temporary and either subside while therapy is still administered or regress after cessation. No evidence of any permanent pathological changes have so far been reported.

Other evidences of the estrogenic activity of stilbestrol are sometimes noted in different clinical conditions. Growth of pubic hair in children or adolescents with hypogonadism and increase in libido in menopausal women are the most common of these.

SUMMARY

Stilbestrol is a powerful and therapeutically effective estrogen.

Gastrointestinal disturbances of unknown etiology are frequent complications of therapy. They are generally temporary but may be persistent.

TABLE 1—*Continued*

Senile vaginitis, cases	Amenorrhea, cases	Dysmenorrhea, cases	Hypoestrinism, cases	G.C. vaginitis, cases	Uterine bleeding, cases	Pregnancy & complications, cases	Mental cases	Miscellaneous	Liver function tests
8			6						
						16			No damage
	6	2							
	12	3							
161	158	38	89	80	505	347	77	75	

Other side reactions such as drowsiness, vertigo and skin rashes sometimes occur.

No permanent toxic effects have been reported from liver function studies, blood or urine chemistry analyses or examinations of blood morphology and blood forming organs.

Overdosage may be responsible for some of the gastrointestinal symptoms and other side reactions. Also uterine bleeding and breast changes may occur but are generally temporary and without significance.

Stilbestrol is very active when given orally or intravaginally but should be used only under the immediate supervision of a physician.

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HOMOSEXUALITY

CRITERIA FOR A HORMONAL EXPLANATION OF THE HOMOSEXUAL[1]

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IN A RECENT ARTICLE Glass, Deuel and Wright[2] compared androgen and estrogen analyses of urine obtained from so-called normal and homosexual males. For the homosexuals they reported androgen-estrogen ratios which they consider "significantly lower than those obtained in 31 normal males."

These conclusions are in line with wide-spread and long-standing popular opinion that homosexual behavior depends on some inherent abnormality which, since the time of the discovery of the sex hormones, is often supposed to be glandular in origin. This assumption is offered as specific explanation in some of the psychology and sociology texts, and some of the psychiatrists are treating homosexuality as an organic disease which is to be cured, if at all, by endocrinologic adjustments. Since these recently published studies are practically the first to test the validity of the current opinion, they are likely to attract some attention; and it is, therefore, desirable to examine the bases of the conclusions and, in fact, to consider the possibility of any hormonal explanation fitting the picture of homosexual behavior as it actually occurs in the human being.

The Glass-Deuel-Wright studies involved androgen and estrogen determinations of single urine samples from 31 supposedly normal males, and two to four samples from each of "17 clinically diagnosed male homosexuals." The summarized data, with some mathematical errors corrected, are as follows.

Samples	Average androgens	Average estrogens	Average of individual ratios
31 Normals	34.1	4.41	12.01
45 Homosexuals	29.9	6.72	7.87
Differences	4.2	2.31	4.14
	±2.46 (S.E.)	±1.08 (S.E.)	±1.85 (S.E.)

The ratios given here represent averages of the ratios obtained from each individual urine sample. Glass, Deuel and Wright introduce an error into their homosexual tables by computing the averages of the several ratios obtained for each individual, and then using the average of all these averages as the final figure for comparison with the normals.

It will be seen that analysis of the table above shows standard errors of such magnitude that the differences can hardly be taken to be conclusive. The samples are small, there is great variation in the samples from different individuals, and in the successive samples from the same individuals. Determinations of androgens in the homosexual group (e.g. *cases 4S, 7S, 14M, 15S*) showed variations of as much as 250 to 350%. Variation in successive measurements of estrogens for some of the homosexuals was as much as 300 to 2,300% (*cases 3S, 5M, 6S, 7S, 8S, 9S, 10S, 14M, 15S, and 16M*). One is not warranted in concluding that the relatively small differences in averages between two such small groups are significant when successive samples from single individuals show 7 to 50 times as much difference.

The published study utilized results obtained by two different methods of collection of the urine. Part of the specimens represented 2-day pooled collections (in the case of the normals) and 5-day pooled collections (for the homosexuals). Part of the samples from each group represented 7 night-and-first-morning specimens. In analyzing their material the authors pooled the results from both methods of sampling. But if the averages for each type of collection are handled separately, the record is as follows.

Samples	Average androgens	Average estrogens	Average of individual ratios
17 homosexuals: 5-day	36.95	8.37	8.44
20 normals: 2-day	34.50	4.86	10.86
Differences	2.45	3.51	−2.42
	±3.51 (S.E.)	±2.08 (S.E.)	±2.59 (S.E.)
28 homosexuals: 7-night-morning	25.69	5.72	7.47
11 normals: 7-night-morning	33.43	3.61	14.10
Differences	−7.74	2.11	−6.63
	±4.01 (S.E.)	±2.40 (S.E.)	±3.36 (S.E.)

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[2] GLASS, S. J., H. J. DEUEL AND C. A. WRIGHT: *Endocrinology* 26: 590. 1940.

By one method of sampling, the homosexual group seems to show more androgen than the normal group, by the other method of sampling there is less androgen. The methods of sampling may have had something to do with the results. In all these cases, however, the differences involve such large standard errors that little significance can be attached to the results.

FIELD DATA ON HOMOSEXUALITY

More basic than any error brought out in the analysis of the above data is the assumption that homosexuality and heterosexuality are two mutually exclusive phenomena emanating from fundamentally and, at least in some cases, inherently different types of individuals. Any classification of individuals as 'homosexuals' or 'normals' (=heterosexuals) carries that implication. It is the popular assumption and the current psychiatric assumption, and the basis for such attempts as have been made to find hormonal explanations for these divergences in human behavior. But what would a study of the phenomena themselves show? Until we know the nature of the gross behavior itself, no hormonal or other explanation is likely to fit the actuality.

Unfortunately there is a paucity of data on homosexual behavior. Our civilization so strongly condemns the behavior that scientific examination of it has hardly begun. The best of the published studies are based on the select homosexual population which is found within prisons, and it seems, heretofore, to have been impossible to discover the extent to which the phenomenon occurs in otherwise socially adjusted portions of the population. At this time, therefore, it seems appropriate to publish certain data which we have collected on homosexuality.

These data are drawn from a series of more than 1,600 histories which we have accumulated in connection with a general study on human sex behavior. Each history covers a minimum of 255 items, and many of the histories cover something more, up to as many as 495 items. All of the histories have been obtained by personal interview. We need ten thousand or more histories before we can draw definite conclusions on most of the phenomena involved. It is imperative that we have complete histories, covering all phases of each individual's sexual behavior, for our interpretation of any part of the picture is dependent upon our knowledge of its relation to the total experience of the individual. The published studies on particular aspects of human sexual behavior sometimes arrive at erroneous conclusions because they do not recognize that total behavior always involves an adjustment in which each item is affected by all of the others in the complex. Our experimentation with the sort of written questionnaire which has been the basis of most of the published studies shows that it is wholly inadequate for discovering any item against which there are strong social taboos. Over 1,300 of the histories were obtained by the present author; 300 of them were collected by Glenn V. Ramsey, of Peoria, Illinois, whose important studies on sexual behavior at the junior and senior high school level are being coordinated with our own on the older age groups. Descriptions of the sampling methods and other technics which are being used in this study will be given in detail at another time, in another place; but here it should be indicated that about 58% of these histories have come from college populations, the remainder from a wide variety of social levels. Over 140 American colleges and universities are represented in the series. Special effort has been made to obtain a representative sample of socially average males and females. The adequacy of the series is being tested by a series of whole samples which represent all of the individuals in particular social groups, such as fraternity and rooming houses, professional and social organizations.

Of the first 1,058 males in our series, 354 have been involved in homosexual behavior. This figure includes only those cases in which one or both parties in the relation have come to ejaculation as a result of stimulation provided by another male. There is another and highly significant group which responds to homosexual stimulation and which, in many cases, has had a considerable amount of homosexual contact, although it has not led to actual orgasm; but for the sake of the present discussion we shall confine our statements to cases which have come to full climax in the relation. This means that over 35.5% of all of the individuals in the series have had one or more homosexual experiences. The figure is a little over 30% for the college-bred portion of the series. Elaborate analyses of these data suggest that they provide a fair basis for estimating the frequency in our American population as a whole, although the validity of this conclusion can only be indicated in the present brief article by citing the figure of 27% obtained from the 329 histories which we have from our whole samples. This last figure is a bit lower than the others, probably because the whole samples are, at present, overloaded with younger ages and with college groups.

At any rate, it seems warranted to believe that something between one-quarter and one-third of all the males in any mixed-aged group has had some homosexual experience.

But, in the course of a lifetime, it is probable that 50% or more of the male population will become involved in homosexuality. In support of this generalization we present the record on the age groups for which we have 50 or more histories per group. The less adequate data which we have for other ages indicate that there may be some further rise in the figures

for the older groups. The figures for the younger groups are summarized in table 1. The figures for the "total adolescent population" represent the total number of individuals in our series who were adolescent as they passed through each age group, up to the age at which the history was reported. The columns marked "with homosexual experience" show the percentage in each age group which has made homosexual contact at any time prior to the date of reporting.

TABLE 1. 1,058 MALES, PERCENTAGE WITH SOME HOMOSEXUAL EXPERIENCE

Age group	Entire series		College population		Whole samples	
	Total adolescent population	With homosexual experience	Total adolescent population	With homosexual experience	Total adolescent population	With homosexual experience
		%		%		%
10	22	9.1	—	—	7	14.3
11	132	16.7	80	15.0	52	17.3
12	445	16.6	273	16.1	161	19.3
13	765	19.2	505	16.2	241	22.4
14	909	23.6	675	19.7	236	22.5
15	883	26.4	699	21.9	214	23.3
16	857	29.1	710	24.5	209	24.4
17	836	29.4	712	25.5	208	24.5
18	805	30.7	709	26.9	205	25.8
19	726	32.1	653	28.5	166	28.3
20	627	32.7	565	29.2	111	28.8
21	520	33.1	465	29.2	80	27.5
22	375	33.9	328	29.3		
23	279	38.0	237	32.9		
24	208	40.8	175	35.4		
25	168	45.8	140	41.4		
26	139	46.0	113	41.6		
27	108	45.4	85	41.2		
28	85	49.5	65	46.2		
29	74	48.7	55	43.6		
30	61	49.2				
31	52	50.0				

The data given above are summarized in figure 1. It will be seen that the whole-sample curve closely coincides with the curve for the college series from which the whole samples were largely derived.

In brief, homosexuality is not the rare phenomenon which it is ordinarily considered to be, but a type of behavior which ultimately may involve as much as half of the whole male population. Any hormonal or other explanation of the phenomenon must take this into account. Any use of so-called normals as controls, in the way in which Glass, Deuel and Wright used them in their measurements, should allow for the possibility that a quarter to a half of these 'normals' may in actuality have had homosexual experience at some time in their lives; and, as we shall show further along, it must similarly be recognized that there are very few 'homosexuals' who have not had at least some, and in many cases a great deal of heterosexual experience.

It is true that many of the individuals in these tabulations have had only a very small amount of homosexual experience incidental to their other sexual activities, while others have had thousands of contacts and exclusively homosexual histories for long periods of their lives. The higher figures come, of course, from older, professional homosexuals who are making daily contacts, and who are regularly capable of repeated climax in a single 24-hour period. The literature constantly makes a sharp distinction between incidental and exclusively homosexual experience, between so-called 'acquired, latent and constitutional homosexuality,' and between 'true inverts' and 'normals.' But although we have more detailed data on a larger number of cases than are recorded in any of the published studies, we fail

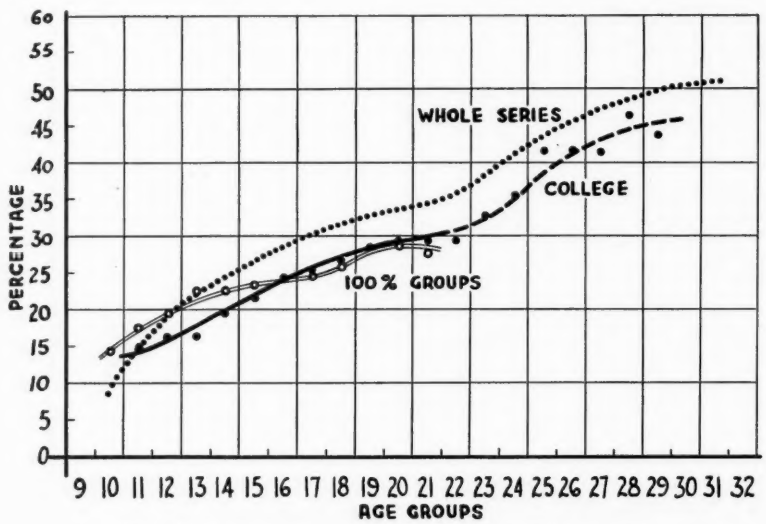

Fig. 1. ACCUMULATIVE CURVE OF INCIDENCE OF HOMOSEXUAL EXPERIENCE. At successive age groups in 1058 males.

to find any basis for recognizing discrete types of homosexual behavior. An analysis on any basis will show every type of intergradation between the extreme cases in our series. There are individuals who have had a lone and more or less accidental experience; there are cases which have had as many as fifteen or twenty thousand homosexual contacts (*cases 2777, 6341*); but between these individuals there are cases which involve all points between one and twenty thousand. There are cases which have confined their homosexuality to a single male partner; in our series there are cases of single males (e.g. *cases 1439, 2777, 4340, 6341, 7434, 7527, 8360*) who have contacted from 1,000 to 15,000 other males. There are cases which began in pre-adolescent sex play, and cases (*0182, 5102, x8661*) which did not begin until after 30 or 40 years of age. We have cases where the homosexuality was confined to a small portion of the life span, a case (*4340*) where it has extended over 60 years of the life span, and other cases which show it extending through periods of every intermediate length. The homosexual may be confined to early or late adolescence, or to the third, or the fourth, or perhaps later decade of life. There are cases in which the homosexual activity was continuous throughout a single period of the history, there are cases where it has been discontinuous with breaks of anything up to 34 years between the periods of participation. A popular opinion bases a classification on the technics involved in the physical relation, and makes a sharp distinction between the so-called active and passive partners in the relation. Many of the so-called 'passives' regularly show that they can respond to homosexual stimulation by coming to climax in the relation. There are popular and even clinical concepts of physical stigmata which are attached to the homosexual; and although there are some 'homosexuals' which show what are popularly considered to be 'effeminate' characteristics, there are others that are physically as robust and as athletically active as the most 'masculine' of men. There are, in short, intergradations between all of these types, whatever the items by which they are classified.

Case No.	Age	Estimated frequency: Homosexual	Estimated frequency: Heterosexual	Percentage homosexual
0104	24	0	450	0
2697	22	4	550	1
7099	19	30	1,000	3
2153	22	15	200	7
6246	24	30	266	10
2433	31	200	1,200	14
8306	22	2,400	10,000	19
7009	25	150	600	20
9053	22	30	100	23
7031	34	800	2,250	26
0892	19	150	300	33
0640	27	1,400	2,400	37
8817	26	350	475	43
3367	26	150	150	50
2463	21	200	200	50
6983	22	200	150	57
7434	24	3,000	2,000	60
6369	26	1,200	700	63
3599	22	100	50	67
8153	21	500	150	77
2777	29	15,000	4,200	78
8460	21	800	200	80
7864	31	1,000	200	83
9924	25	700	100	88
3687	27	1,250	100	93
7841	29	2,000	100	95
8837	41	3,000	100	97
0168	19	500	4	99
4047	24	1,600	0	100
2432	29	4,000	0	100

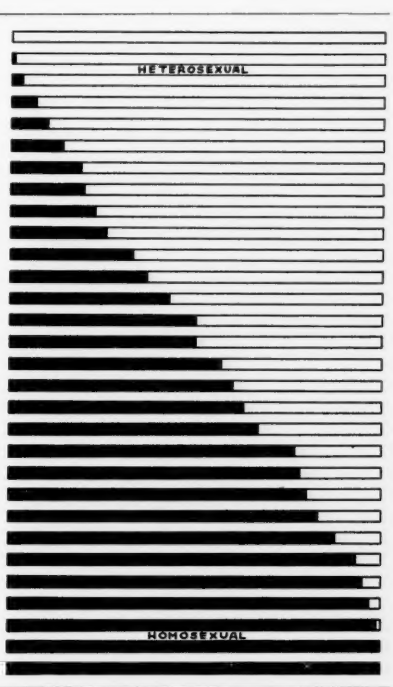

Fig. 2. COMBINATIONS OF HETEROSEXUAL-HOMOSEXUAL EXPERIENCE. Showing every gradation between exclusively heterosexual and exclusively homosexual experience in a selected series of 30 males.

In this paper, only a single instance of intergradation can be presented in more detail. This involves the proportion in which the homosexual and the heterosexual fit into the life of a single individual. For while there are individuals who are exclusively heterosexual, or exclusively homosexual, there are many who carry on both types of activity, sometimes suc-

cessively at different periods in their lives, more often simultaneously in a single period of the life span. This is illustrated by the series of 30 cases shown in figure 2. The chart is based on the percentage frequency of orgasm (actual ejaculation) inspired by human social contacts (in distinction to such auto-sexual outlets as masturbation and nocturnal emissions). It includes cases in which the homosexual has provided only a small proportion of the outlet, cases in which the homosexual and heterosexual have contributed more or less equally to the picture, cases in which the homosexual has provided the whole of the socialized outlet, and every type of case between the extremes. It will be seen that one of the most actively homosexual cases in the series (*case 2777*) is a male with some 15,000 male contacts, and a concurrent heterosexual element which includes intercourse an estimated four or five thousand times.

The curves showing the frequencies in these various types of the heterosexual-homosexual balance are different for various age groups in our series. In general, cases in which the heterosexual-homosexual ratio is near 50:50 are more abundant in the earlier age groups; those in which the homosexual or heterosexual are more nearly exclusive are more frequent in the older groups. There is evidence that the transformation to the more frequently exclusive pattern of the older individuals is partly the result of psychic conditioning, partly the result of social pressure which fixes the heterosexual by custom and by law, but which as effectively fixes the homosexual by ostracizing the individual who departs from the accepted mores. We are particularly indebted to the Ramsey series of histories for the interesting material on the younger age groups. The detailed record back of these generalizations must be published elsewhere.

It should be more generally understood that there are many cases of individuals who regularly include both the heterosexual and the homosexual among their activities in the course of any month, week, or day. We have cases (e.g. *2777, 4651, 6341, 8306*) in which both types of contacts were successfully made in the course of a single hour.

Finally, it must be realized that an exclusively homosexual or exclusively heterosexual pattern may be replaced at a later period in the life of a single individual by more or less exclusive activity in the other direction. Of the first 108 individuals in our series who have had more than 100 homosexual contacts each, 55 (=51.%) have made distinctly successful heterosexual adjustments. There are two cases of males (*cases 3063, 8360*) who had had 15 and 17 years of almost exclusively homosexual experience, who at ages 30 and 28 (respectively) began practically exclusive heterosexual activities which involved intercourse 3 to 7 times per week. On the other hand, we have a few cases (e.g. males *7504, 8425, 9957*, females *0632, 2302, 4541, 6367*) in which exclusively heterosexual activities were abandoned within a brief span of time for more or less exclusively homosexual activities.

Throughout the case histories, the circumstances of the first sexual experience, psychic conditioning, and social pressures are obvious factors in determining the pattern of the behavior. It would appear that no similar correlation has as yet been shown between hormones and homosexual activity. It is, of course, not impossible that endocrines are involved; but in order to demonstrate that, it would be necessary to show a correlative variation in hormones and behavior which includes such gradations, combined patterns, and changes of pattern as have been described here.

SUMMARY

Glass, Deuel and Wright report androgen content and androgen-estrogen ratios in male homosexuals which are lower than those in a 'normal' control group. Their conclusions are invalidated by the small size of their series, by the great variation shown among the individuals in the series and in successive samples from single individuals, and by the contradictory results which were obtained by the two different technics of securing urine samples.

Any hormonal or other explanation of the homosexual must allow for the fact that something between a quarter and a half of all males have demonstrated their capacity to respond to homosexual stimuli; that the picture is one of endless intergradation between every combination of homosexuality and heterosexuality; that it is impossible to distinguish so-called acquired, latent, and congenital types; and that there is every gradation between so-called actives and passives in a homosexual relation.

Any hormonal or other explanation of the homosexual must allow for the fact that both homosexual and heterosexual activities may occur coincidentally in a single period in the life of a single individual; and that exclusive activities of any one type may be exchanged, in the brief span of a few days or a few weeks, for an exclusive pattern of the other type, or into a combination pattern which embraces the two types.

Any explanation of the homosexual must recognize that a large portion of the younger adolescents demonstrates the capacity to react to both homosexual and heterosexual stimuli; that there is a fair number of adults who show this same capacity; and that there is only a gradual development of the exclusively homosexual or exclusively heterosexual patterns which predominate among older adults.

The Administration and the Dean of the Graduate School of Indiana University are responsible for a part of the financial support of these studies. Glenn V. Ramsey, Boys Health Director in a high school at Peoria, Illinois, secured the very important series of histories which we have on the youngest age groups. Clyde E. Martin is responsible for the intelligent and careful handling of our files and for the extensive computations which have been involved in the analyses of the data. My wife, Clara McMillen Kinsey, has materially contributed to our interpretations of the case histories and their objective treatment in this study.

HERMAPHRODISM

BILATERAL OVOTESTES WITH SUPRARENAL-LIKE REMNANTS

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THE TERM, true hermaphrodism, is restricted to those individuals who have gonads characteristic of both sexes, that is both male and female formed elements in either one or both gonads. The type of hermaphrodism seen in lower forms as a usual feature in reproduction does not occur in vertebrates, although non-functioning types are not infrequently reported for pigs and goats (2, 3) as well as man (4). Witschi (1) states "the true hermaphrodite is characterized by the co-existence of ovarian and testicular tissue . . . whether or not one requires the presence of spermatogonia for the recognition of testicular character is purely a matter of terminology." No functional hermaphrodite has been described in man.

The patient herein presented was referred to the endocrine division in 1938 at the age of 20.

J.M. was an only child of a mother who had begun to menstruate at the age of 18 and who ceased menstruating at 37. During the first 4 months of the pregnancy she had been confined to bed because of backaches. Eleven years after the birth of this daughter, during an operation for appendicitis, no significant pelvic pathology was found.

The external genitalia at birth consisted of an apparently normal vulva and protruding therefrom an organ resembling a penis about 2½ cm. long. There was no urethral opening in this organ. She was reared as a female. Her early development was otherwise apparently normal.

The patient experienced a doubtful, painless menstrual period at the age of 13 and a similar spotting at the age of 15 lasting for one day. Until the age of 18, she had abdominal cramps and nausea each month without any vaginal bleeding. No female breast tissue development had ever been observed.

As the patient grew older the peno-clitoris assumed the usual proportions of the male structure. She experienced pleasurable sensations on manipulation of this organ once weekly. She was, however, attracted toward males and had no sexual desire for females.

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At the age of 17, the embarrassment of this peno-clitoris when undraped in the presence of other females, and the desire for a future marriage led her to seek medical advice. In August of 1935, the organ, which at that time presented a chordae adherent to the rudimentary labia minora, was removed. It originated at the upper angle of the vulva at the usual site of a penis or clitoris. Relaxed it measured 7 × 2.5 × 2 cm. and had a prepuce and well developed corona upon the glans. A blind ridge was found upon the dorsal surface. The organ contained corpora cavernosa and spongiosa but no urethra (fig. 1). The urethral opening was in the vestibule. The labia minora were normal, the vaginal orifice admitted two fingers and upon speculum examination revealed a dimple considered to be the external cervical os.

Her psychology remained essentially female. She became quite intimate with a male friend over a period of a few months. She was strongly attracted to him and physical contact gave her a general feeling of warmth and a pleasureable sensation. Her general health had been good. Some constipation was present. She also had an indefinite pain, often cramp-like in nature, in the right flank and lower abdomen radiating to the opposite side.

Physical examination. The patient was tall and thin, somewhat apprehensive and spoke in a low pitched voice. Physical measurements were: height, 66 in.; span, 67¾ in.; lower measurement, 32¾ in. Pulse was 84 per minute, blood pressure, 122/90. Her weight was 110 lb.

Her intelligence appeared to be somewhat below normal. Her skin was coarse and dry, the face long, thin and bony. The narrow pointed chin had three fine fat folds below it. The nose was long. Slight hairiness was present on the upper lip. Many teeth were missing. The neck was long. The thyroid was palpably enlarged and slightly nodular. The shoulders and body configuration were masculine. The breasts displayed no glandular development; the areola and nipples were male in type. The abdomen was thin. Sparse, thick, heavy, long hairs were present over the pubic line. The extremities were long and thin with hair upon them. The external genitalia have been described.

Laboratory data (12/7/38). Blood chemical tests re-

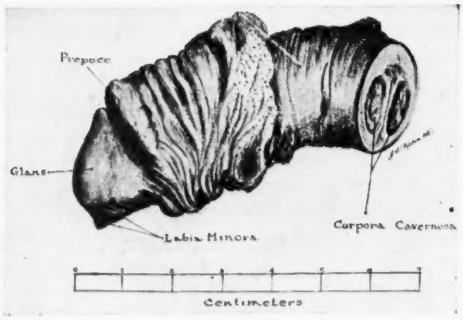

Fig. 1. Penoclitoris removed at age of 17 Years, August, 1935.

sulted in the following: sugar, 115 mg. %; urea, 14.1 mg. %; cholesterol, 178 mg. %; chloride, 357 mg. %; potassium, 16.4 mg. %; calcium, 10.5 mg. %; phosphorus, 2.6 mg. %; phosphatase, 6.1 Bodansky units.

Sugar tolerance test result (1/5/39) was as follows:

8:30	103 mg. %	fasting
9:30	165 mg. %	1 hour
10:30	123 mg. %	2 hours
11:30	101 mg. %	3 hours

The basal metabolic rate on 12/14/38 was 3% below normal. The urinary hormone excretion[1] on 12/8/38 was: prolan, +; no estrin found by a modified Kurzrok technic; androgens, 6 capon units (in 72 hours).[2]

Vaginal PH and vaginal smear were as follows:

	12/16/38	12/23	12/30	1/6/39[4]	4/3	4/10	5/15	7/17
Vaginal PH	7.5	8.	8.	8.	8	8	5	4
Vaginal smear[3]	+	o	o	+	+++	++++	++++	++++

X-ray examination revealed an android type of pelvis with calcified shadows in the region of the ovaries.

Because of the general clinical picture and the presence of the calcified areas in the pelvis, exploratory laparotomy was advised. An infantile uterus measuring 3 ×3.5 ×2 cm. lay in the midpelvis. Small but proportionately normal appearing tubes and pelvic ligaments were seen. The gonads lay in proper relationship to the fimbriated ends of the tubes. The right gonad was against the lateral pelvic wall and measured 3.5 ×2.5 ×1.5 cm. It was irregular in shape, gray white in color and gave the appearance of being atretic with only slight depressions on the surface. At the lower end of the gonad, on section, was a circumscribed gray white nodule 1.5 cm. in diameter; this contained calcified areas. The left gonad was in the pelvis and measured 4 ×2.5 ×2 cm. and was similar to the right. Wedge shaped sections were taken throughout the length of each ovary. These exhibited three types of tissue as follows.

1. Dense hyalinized ovarian stroma containing many calcium deposits arranged in such a fashion as to suggest calcification of primordial follicles. A few poorly defined bony trabeculae were seen. No follicular elements or germinal epithelium was noted. A few fibrotic areas were suggestive of corpora albicantiae.
2. Adrenal cortical-like tissue whose cells showed marked variation in size and staining qualities.
3. Apparent testicular tissue.

Because of the presence of intermixed gonadal tissue, and because the patient was psychologically a female, and thirdly because of the possibility of a malignant change in the adrenal cortical areas, removal of both gonads and subsequent administration of estrogens was advised.

After removal, both gonads revealed a similar picture. An occasional area of hyalinized fibrotic tissue suggesting the form of corpora albicantiae were seen. In other areas cords and strands of large mononuclear cells with vesicular nuclei and scant cytoplasm resembling the suprarenal cortical tissue were noted. In another section of each gonad, tubules lined by columnar cells were found, heaped up and occasionally embedded in a loose hyalinizing connective tissue stroma. These resembled seminiferous tubular tissue. Interstitial cells were numerous (fig. 2–5). The pathological picture was that of gonads containing testicular tissue, suprarenal-like tissue with zones of potential malignancy and ovarian tissue with areas of degeneration. No definite follicular elements were seen.

Following the removal of the gonads estrogens were administered, the patient receiving about one and one-half million I.U. in the ensuing 8 months. Dosage was administered by hypodermic, by mouth and by inunction to the breast. She gained weight, became generally rounded out and for the first time developed female breasts. Her voice became higher pitched and the actions more decidedly feminine. She expressed a desire to bear children after an uncontemplated marriage. The vaginal smear and PH became normal. At the present time, 21 months after operation she is receiving estrogens by inunction only and is maintaining her breasts and feminine demeanor.

DISCUSSION

We have presented an individual having male and female formed elements in both gonads, bilateral ovotestes. The secondary expressions, first noted at birth, were characteristic of both sexes; viz. the penoclitoris, the masculine structure, the deeper voice,

[1] *Assay methods. Prolan A, B.* A morning specimen of urine is filtered and made acid in reaction with a few drops of acetic acid. A 47 cc. portion is mixed with 188 cc. of 95% alcohol, shaken for 10 minutes and allowed to stand 2 hours or longer. The precipitate, collected by centrifugation is washed with 20 cc. of ether (to remove toxins and estrogens), then dried and suspended in 7 cc. of water. After centrifuging, the water extract is injected into immature female mice, 6–8 gm. in weight. Two mice are given 0.12 cc. twice daily for 3 days, and 2 mice are given 0.25 cc. twice daily for 3 days. The ovaries of the mice are examined 96 to 100 hours after the first injection.

Estrogen. A 500 cc. portion of a 24-hour specimen, made to PH 1.2–1.5 with HCl, is extracted twice with 300 cc. of petroleum ether. The combined ether fractions are evaporated and the residue dissolved in 7 cc. of sesame oil. Three ovariectomized rats (175 gm. weight) are injected with 0.12, 0.25 and 0.5 cc., respectively, twice daily for 2 days. Vaginal smears are examined on the third and fourth days. The smallest amount giving a cornification reaction is 1 R.U.

[2] Courtesy of Dr. Darby, Presbyterian Hospital.

[3] Vaginal smear expressed in terms of cornification.

[4] Operation 1/11/39, the last 4 determinations followed large doses of estrogenic substance.

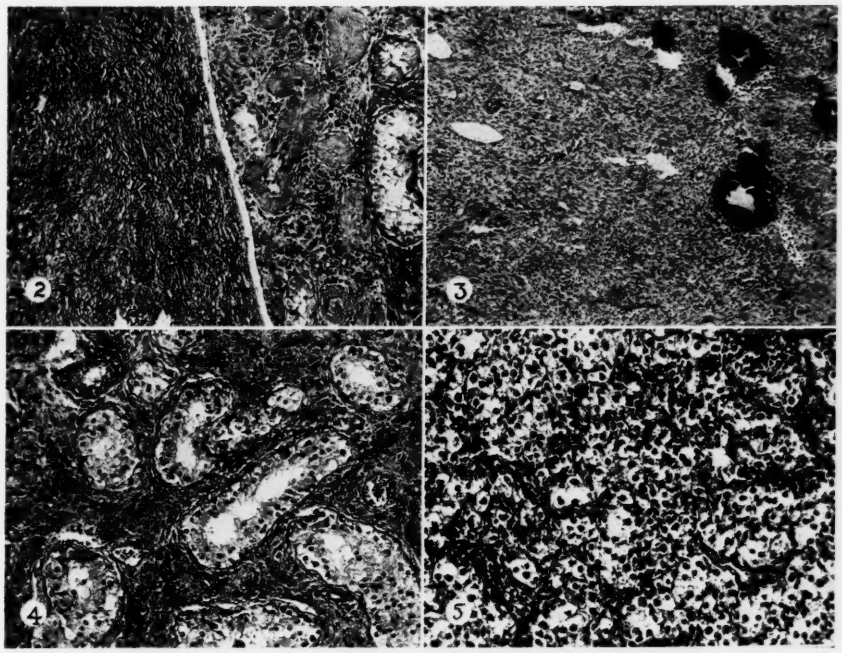

Fig. 2. Gonad section at boundary of ovarian and testicular portion. ×50. Fig. 3. Gonad. Ovarian stroma with calcification suggesting degenerated primordial follicles. This calcification was profuse in the ovarian portion of the gland. ×100. Fig. 4. Gonad. Testicular tissue. Tubules lined by heaped up columnar cells. Interstitial cells are numerous. ×125. Fig. 5. Gonad. Suprarenal cortical-like tissue, cords and strands of large mononuclear cells. ×160.

and absence of breasts, together with labiae, a vagina, uterus, tubes and a female psychology.

A controversial point, we believe may arise in the histology of the gonad. Both Marine and Helpern to whom sections were submitted concur in the opinion that the tubular elements represent seminiferous tubules. Gudernatsch (5) raised the question, previously present in our minds, of terming the tissue ovarian in the absence of definite germinal epithelium. We, however, consider the presence of corpora albicantiae indicative of previously active follicular tissue. Furthermore the arrangement of the calcium deposits in the ovarian stroma is suggestive of calcified degenerated primordial follicles. It is of further interest that this calcium had sufficient mass to cast significant radiographic shadows. The ossification occurred secondarily. We feel that the adreno-cortical tissue is an embryonal remnant. Its bilateral location in the sex organs indicates that the disturbance was not primarily zygotic. We assume that an autosomal derangement of the embryonal tissue took place, akin to other congenital anomalies. Since this adrenal tissue in embryonal life is part of the mesodermal blastema and has a masculinizing influence, it is conceivable that its action upon the undifferentiated gonad converted a genetic female into an intersex.

The chemistry of the androgens and estrogens in hermaphrodites has been incompletely studied. We found prolan but no estrin in the urine. Six capon units of androgens were found in a 72-hour specimen of her urine. These findings indicate a hypoactivity of the gonads and consequent increase in the usually suppressed prolan.

The procedure in our case was determined by the psychological, sociological and histological aspects. Despite her masculine appearance and bony structure, the patient had been reared as a girl. She had all the interests and desires of a female. She was attracted toward the male sex and had hopes of becoming a wife and mother. The failure of breast development, the enlarged clitoris and the amenorrhea were only sources of embarrassment to her. The fact that she might be a male was farthest from her thoughts. Accentuating her male characteristics must surely have precipitated a severe emotional upheaval. The histological findings of testicular tissue, apparently inert ovarian tissue and a possibly malignant adrenal cortical tissue guided us in our decision to castrate

the patient and then administer estrogens to develop the latent female characteristics.

SUMMARY

A case of human hermaphrodism is presented.

Both gonads contained (*a*) fibrotic, calcified and ossified ovarian stroma in which occasional corpora albicantiae were seen; (*b*) seminiferous tubules and (*c*) adreno-cortical tissue exhibiting signs of cellular overactivity. The suprarenal tissue was probably embryonal and may have been the determining factor in the hermaphrodism.

The treatment consisted of castration followed by the administration of estrogens, intramuscularly, perorally and percutaneously over the breasts. The breasts, body contour and demeanor developed a more feminine character. The psychic response prompted the discontinuance of this feminizing program.

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SEX HORMONE EXCRETION

THE SEX CYCLE OF A NORMAL WOMAN[1]

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THE IMPORTANCE of determining the hormonal output of normal women hardly needs to be emphasized. To the clinician attempting to diagnose abnormalities of sexual functions on this basis, the establishment of normal values is essential. Insofar as this approach may contribute to our knowledge of reproductive physiology, especially to the much-debated question of the time of ovulation, it is of practical concern to many. No doubt other methods, uterine motility tests, biopsies and laparotomy findings will provide needed information; nevertheless, the method of urine assays is a promising one. The three types of hormones primarily involved, gonadotropin, estrogens and progestin (as pregnandiol), are excreted in the urine and their concentrations may be followed. Further, long-time studies on the same subject are possible only by this method.

As is true in so many studies of this sort, the establishment of the 'normal' presents difficulties. The fact of individual variation in all functions, plus the admitted complexity of the female reproductive cycle would justify the prediction that variation within normal limits would be frequent. Work done so far supports this preconception. It appears, therefore, that before definite statements concerning 'normal' hormone levels may be made and conclusions based on this information be reached a great deal of data must first be accumulated. Studies of this sort are tedious and the gathering of data will necessarily be slow. This paper is presented merely as a contribution to this slowly accumulating store of knowledge.

The subject concerned in this study, Mrs. *L. W.*, age 39, we presume to consider normal on the basis of the following criteria.

1. She is a married women of demonstrated fertility (being the mother of three children) in whom pregnancy occurred without undue lapse of time. All births were normal.

2. Her menstrual history is normal. The age at onset was 15 years, the periods were regular, the average length of 81 cycles over a period of 6 years, 1933–1938 inclusive, being 26.6 days (minimum 23, maximum 32 days) the duration of flow is 4 to 5 days, in moderate amounts, the periods are painless.

3. Her physical history is normal. Childhood diseases which she had are whooping cough, scarlet fever and measles. As an adult she had pneumonia following influenza, and two operations, tonsillectomy and repair after childbirth.

EXPERIMENTAL

Hormonal assays. The daily output of gonadotropic hormone was determined during 18 consecutive menstrual cycles and the daily output of estrogen during the last 9 was determined. Details of the procedure will be published elsewhere. For the first 9 cycles the results are shown in figure 1, for the last 9 in figure 2. Vaginal temperature readings were made each morning just before arising; these results are also included in figure 2.

Figure 2 includes 3 elements, the gonadotropic hormone output (upper line), the estrogen output (middle line), and the daily vaginal temperatures (lower line), for the same 9 cycles. "M" represents menstruation. The upper solid line indicates the average rat uterine weight, in milligrams, with doses of 3-hour urinary excretion. Where positive reactions occurred, a dotted line immediately below shows the uterine response to half the dose, i.e., with 1½-hour excretion. The middle solid line gives the percentage response (vaginal cornification in adult castrate females), of estrogen in doses of 1-hour urinary excretion per rat. Again the dotted line immediately below shows the response on half the dose, i. e., ½-hour excretion. The third line represents the vaginal temperature.

Reaction time and association time tests. Daily tests of the reaction time (50 responses to visual stimuli) and the association time (50 words from the Kent-Rosanoff tables) were carried out. We hoped, in spite of the many extraneous factors which would affect such testing, to find a variation consistent with the endocrine rhythm or with menstruation. This hope

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[1] This investigation was supported by a grant from the Penrose Fund of the American Philosophical Society.

was not realized. Either outside influences are too strong or the endocrine fluctuations are not mirrored in the neuro-muscular and association systems.

Personal observations. A careful daily record was kept of subjective experiences. These observations may be briefly summarized. No 'mittelschmerz' was ever noted. No correlation between positive hormonal responses and coitus could be found. Sexual desire was strong during the mid-cycle but equally strong just after menstruation, when positive reactions seldom occurred. A head-ache centering on the right side of the nose and the right eye frequently occurred just preceding or following a positive gonadotropic reaction but was noted occasionally at other times as well. All in all, in spite of intelligent introspective observation, nothing in the physical condition, mental state or sexual life could with any assurance be associated with the endocrine rhythm as registered in the urinary assays.

Experience with estrogen administration. Although estrogens are widely used in the treatment of disorders associated with the menopause, and sometimes intermittently in menstrual disturbances, little information is available concerning possible effects of long-time estrogen administration on the normal cycle. Because her normal hormone output and menstrual history had already been well established this subject appeared an ideal one for such a study. The estrogen chosen was estradiol, which was administered percutaneously (being applied to the skin of the face and neck once daily, upon retiring) in a dose of 0.04 mg. daily. Administration was begun September 16, 1938, this being the beginning of the 5th cycle in figure 2.

No objective findings were noted during the first 2 cycles. On the 14th day of the third cycle, however, the excretion of a blood-stained, mucous discharge began. The amount of discharge was sufficiently great to require the use of pads. This discharge continued uninterruptedly for 17 consecutive days. There were, however, variations in amount. After 3 days of this discharge (on the 17th day of the cycle), the flow became more profuse, resembling that of a typical menstruation. At this time the administration of the estrogen was discontinued. This period of profuse flow lasted 3 days and then subsided, but the bloody, mucous discharge continued. After 6 more days of this (on the 26th day of the cycle) the flow became extremely profuse, much greater than the subject had ever previously experienced. Many large blood clots were expelled. This occurred at the time when normal menstruation might have been expected. The following cycle showed lesser abnormalities. On the 11th day there was again a red, mucous discharge which lasted 2 days and on the 21st day the same type of discharge was noted, continuing in this case for 5

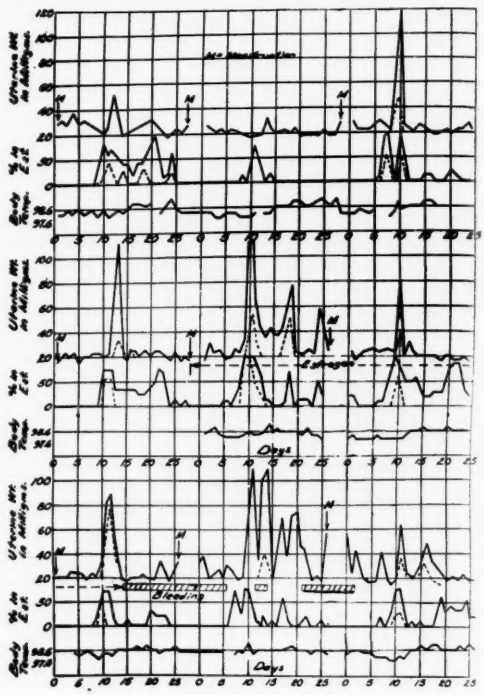

Fig. 1, 2, 3,

days, at which time menstruation began. Nothing of the sort has occurred since, menstruation having been normal for the ensuing two years. This eliminates any possibility of menopausal onset as responsible for the occurrence.

A slight dyskeratosis on the subject's neck which had been present for years but had shown no previous tendency to grow, began to grow rapidly following the administration of estrogen. It was diagnosed on June 9, 1939, as an epithelioma by a leading dermatologist and removed by him. It must be remembered that the estrogen was rubbed into the skin of this region nightly for 2 months.

DISCUSSION

Several interesting points appear in the factual data. If the appearance of a strongly positive gonadotropic reaction indicates ovulation (this is, of course, not proved, either for this or any other indirect test), then this phenomenon occurred more than once in several cycles. As regards estrogen the occurrence of 2 peaks, noted in the thorough work of Gustavson et al. (1) and others, was generally confirmed.

A most significant point, we believe, concerns the estrogen-gonadotropic hormone relationship. Almost invariably it was found that the estrogen excretion starts upward from 1 to several days before the

gonadotropic peak occurs. We venture the suggestion that this primary estrogen output stimulates the hypophysis to liberate gonadotropic hormone and thus brings about ovulation. The question of estrogenic action on the hypophysis is a debated one, but some opinion tends to the view that the primary effect is a stimulating one, although long-continued administration results in inhibition. The second estrogen wave may or may not be followed by a gonadotropic peak. If one assumed that the first peak resulted in ovulation, progestin secreted by the resultant corpus luteum must be reckoned with. Progestin is believed to inhibit the estrous cycle and ovulation (2) and it is therefore possible that it may have an antagonistic effect upon the estrogen produced during the second wave, preventing it from stimulating a further release of gonadotropic hormone. In those cycles in which a second gonadotropic peak occurs it may be that an insufficient amount of progestin had been produced to completely arrest the action of estrogen. This emphasizes the importance of simultaneous progestin (pregnandiol) determinations and also underscores again the central theme of this paper, namely, that the human reproductive cycle is an extremely complex thing requiring much further work before conclusions are possible.

There are, unfortunately, several gaps in the body temperature data. In general, it appears that the average temperature was low during the first half of the cycle and higher during the second. No sharp break at the time of presumed ovulation was noted.

SUMMARY

Studies of estrogen and gonadotropic hormone excretion, body temperature determinations, tests of nervous system function and subjective findings, in a normal woman, are herewith reported.

More than one gonadotropic hormone peak occurred in a number of cycles. Estrogen excretion occurred in 2 waves, usually preceding the gonadotropic peaks. A theory of the control of ovulation is suggested on this basis. Vaginal temperature findings were inconclusive. Reaction and association time fluctuations could not be correlated with hormone fluctuations. Nothing in the sex life of the subject, nor in her physical or mental state could be correlated with hormone findings. The effects of estrogen administration are described.

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HYPOPITUITARISM

SIMMONDS' DISEASE ASSOCIATED WITH PERNICIOUS ANEMIA, WITH BIOASSAY OF LARGE CHROMOPHOBE ADENOMA

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THE VITAL ROLE of physiologic fundamentals in the advancement of knowledge of certain problems in clinical medicine is well illustrated by the remarkable progress in the field of endocrine medicine during recent years. For example, pituitary tumors have been recognized pathologically since the time of Morgagni (1), and their clinical symptoms were anticipated as early as 1850 by Orr (2), Abercrombie (3), Zenker (4) and others, but the first evidence of the far-reaching influence of the pituitary gland awaited the early experiments of the late Harvey Cushing (5). These important contributions presaged the first description of the clinical syndrome of pituitary deficiency by Simmonds (6) in 1914.

This symptom complex coincides in every detail with the changes observed in laboratory animals following extirpation of the anterior hypophysis. As a rule the symptoms of pituitary failure as observed clinically develop insidiously, but in profound shock such as is encountered during post-partum hemorrhage, acute hypophyseal necrosis has been demonstrated (7). Many of the symptoms observed can be traced directly to hypofunction of subsidiary glands: *a*), gonadal failure with atrophy, loss of libido, amenorrhea, and menopausal complex, *b*), secondary hypothyroidism; and *c*), hypoadrenia with low blood pressure, disturbances in electrolyte balance and in the metabolism of glucose. To these we must add *d*), a group of related symptoms such as weakness, loss of weight, and changes in the integument—symptoms which are probably related to dysfunction of all units in the endocrine system. It would seem that anorexia and cachexia have been overemphasized as symptoms of pituitary deficiency, for it is apparent both clinically and from laboratory studies that neither symptom may ever appear in a large number of cases.

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Although Simmonds' disease was immediately recognized as a clinical entity, few cases were diagnosed until the more important features of pituitary physiology were clearly demonstrated (8). Since that time several hundred cases have been reported under this title, but the tendency to include functional pituitary disorders (9, 10, 11) in this group has led discriminating clinicians to segregate those cases with proved pituitary lesions (19, 13). This has promoted a better understanding of the incidence of these cases, and has tended to support Berblinger's, observations (12) concerning the rarity of this disease. (Berblinger sectioned more than 10,000 pituitary glands obtained at routine necropsy before a typical fibrotic lesion was found.)

Recent summaries of the literature (13) indicate that there were approximately 70 verified cases of this disorder reported by April, 1938. Since that time 16 additional verified cases have been reported (atrophy and necrosis, 6 cases (7, 14–17) cystic tumors, 9 cases (18–22); syphilis?, 1 case, (23). The largest single group of confirmed cases yet reported was presented recently by Stephens (18) who also described for the first time the series of symptoms developing in man subsequent to destruction of the hypophysis.

The case here reported emphasizes three interesting aspects of pituitary physiology: further evidence indicating a profound insufficiency of adrenal function as an etiologic factor in the more vital disturbances of pituitary deficiency states; the functional role of the chromophobe adenoma as determined by assay methods; and the possible relation of the pituitary to hemopoiesis.

CASE REPORT

A white man, aged 62 years, first came under observation in August, 1938. A chronologic survey of his symptoms reveals that approximately 20 years (1918) previously he had first complained of headaches. These were intermittent and were localized to bifrontal and bitemporal areas. They did not incapacitate the patient, but later

became associated with weakness, increased fatigability and paresthesias involving the lower extremities. There was a gradual progression in these complaints until 1930 when a series of gastrointestinal symptoms supervened. These were characterized by anorexia and attacks of vomiting which were followed by profound prostration and weakness of such a degree that the patient "could not speak above a whisper." These episodes occurred about every 6 months and required several weeks' rest in bed for recovery. Investigations by various physicians and clinics demonstrated moderate normochromic anemia (4,000,000 erythrocytes per cu. mm. of blood) associated with achlorhydria. There was symptomatic improvement after administration of liver capsules and hydrochloric acid.

In 1932 the gastrointestinal symptoms returned and cholecystectomy was performed. It was followed by alarming prostration, weakness and prolonged convalescence. Shortly afterward hot flushes, occurring 4 to 5 times daily developed; the patient became emotionally unstable; there was a gradual loss of hair over the face, axillae and pubis; and finally there was total impotence. At about the same time there were transient attacks of polydipsia and polyuria. The anemia persisted at about the same level. Various urologic studies were made but no diagnosis was established until 1937 when a thorough study revealed normochromic anemia (erythrocyte count 3,700,000), achlorhydria and reduced vibratory sensation for the lower extremities. When liver therapy was administered there was some improvement in the patient's general condition until August, 1938, when he was admitted to the Neurological Service because of paranoid ideas with reference to his wife, who was 60 years of age. These ideas apparently dated from the onset of impotence, and shortly before admission the patient attempted to strangle his wife.

Other symptoms included dyspnea on moderate exertion, palpitation and precordial pain with overexertion or overeating, and severe cramps of the lower extremities at night. During the past 15 years the patient's weight had gradually declined from 160 lb. (72.6 kg.) to approximately 115 lb. (52.2 kg.).

On physical examination there was a peculiar translucent pallor that was out of all proportion to the moderate anemia previously observed. The voice was high pitched and definitely feminine in character. There was no hair over the face, axillae or pubic region. The eyebrows were thin and the hair on the scalp was fine and silky. Other pertinent findings included gross defects in the field of vision involving bilaterally the superior and temporal quadrants. The retinal as well as other peripheral vessels showed moderate sclerosis. There was moderate bilateral impairment of hearing not associated with involvement of the middle ear. The marginal papillae of the tongue were thinned out and atrophic. There was no definite baldness. Examination of the chest revealed moderate senile emphysema, but the chest was otherwise normal. The blood pressure was 130 mm. of mercury systolic and 80 mm. diastolic. The genitalia showed complete atrophy, the testes being soft and doughy and measuring 23 ×11 ×8 mm. The prostate gland, which had been described as being enlarged in 1934, was very small. The results of neurologic examination were essentially negative except for the visual field defect and slight reduction in vibratory sensation for the lower extremities.

The laboratory findings in this case included a concentration of hemoglobin of 9.5 gm. in 100 cc. of blood, erythrocyte count of 3,500,000, and total leucocyte count of 8,600 with 37% neutrophils, 56% lymphocytes, 2% monocytes and 5% eosinophils. The reticulocyte count was 0.6%, platelets numbered 230,000 per cu. mm. of blood, bleeding and coagulation findings were normal and clot retraction was normal. The individual cell volume was 97.3 cubic microns and volume index 1.01. The results of urinalysis were normal except for occasional pyuria. Fasting blood sugar levels ranged from 58 to 84 mg. in 100 cc. of blood, and non-protein nitrogen from 27 to 34 mg. in 100 cc. of serum. Serum protein levels ranged from 4.4 to 5.0 gm. in 100 cc. with the albumin-globulin ratio approximating 1.7 to 1. The serum calcium was 10.0 mg. in 100 cc. and phosphorus was 3.5 to 4.5 mg. The cholesterol level varied from 115 to 175 mg. in 100 cc. of plasma. A single determination of uric-acid level for whole blood was 2.65 mg. in 100 cc. The 24-hour excretion of creatinine approximated 1.637 gm. (preformed creatinine 0.8 gm., creatinine 0.837 gm.), while the excretion of creatine was 0.430 gm. The B.M.R. on admission was −20%. Gastric aspiration in another clinic demonstrated achlorhydria in 1920, 1929 and 1934. This persisted throughout our period of observation.

Oral and intravenous glucose tolerance curves suggested an impairment in the absorptive mechanism of the bowel as shown by a flat oral tolerance curve. The blood sugar level after oral administration of 50 gm. of glucose was rarely higher than 90 mg., and intravenous tolerance curves were entirely normal. The chloride excretion test as described by Wilder and others (24) for detecting impaired function of the adrenal cortex showed a range in excretion level of sodium chloride from 157 mg. per 100 cc. to 300 mg. per 100 cc. of urine during the first 24-hour period. The final 4-hour specimen showed a range of 233 mg. to 367 mg. per 100 cc. of urine. Ophthalmologic examination confirmed the bitemporal quadrant defect in the field of vision. Stereoscopic roentgenograms of the skull demonstrated a round intrasellar mass about 3 cm. in diameter which had eroded the clinoid processes, and inferiorly had obliterated the sphenoid sinus. Roentgenograms of the chest and gastrointestinal tract were normal.

The first treatment was irradiation through bitemporal and glabellar fields in a dose of 150 r. (1.35 mm.) for 6 daily exposures during the first week in September, 1938. This did not result in improvement of the patients symptoms and there was a progression in the visual field defect.

Since the patient's general condition was too poor for any surgical procedure, an attempt was made to evaluate various forms of substitutional therapy. A basic diet which was high in carbohydrate and vitamins was supplemented by parenteral administration of thiamin chloride (50 mg. daily), hard candy at the bedside and other measures as indicated. A growth hormone mixture[2] was first injected subcutaneously in a dose of 2 cc. (80 growth

[2] Polyansin.

units) daily. Within 5 days there was marked improvement in vigor, general strength and degree of activity. The patient began taking hikes in the afternoon. His B.M.R. rose from −20% to +9%. This response was relatively brief, however, and after 2 weeks the B.M.R. was −18%. After one month the supply of the pituitary extract was exhausted and other material[3] (dose 4 to 8 cc., 40 to 80 U, daily) substituted. There was no significant change, however, and after 3 weeks, administration of the original pituitary extract was resumed. In spite of higher doses the B.M.R. remained at levels ranging from −22% to −26%. The weakness, sensitivity to cold and other symptoms progressed gradually so that by December, 1938, the patient was bedridden most of the time.

As previously mentioned, there was an abnormal increase in the elimination of chlorides in the form of sodium chloride in response to Cutler's test for adrenal insufficiency. The first chloride excretion test showed a level of 157 mg. of sodium chloride per 100 cc. of urine for the 24-hour specimen while the 4-hour specimen contained 233 mg. of sodium chloride per 100 cc. It was felt that these figures were of considerable significance, more because of the increasing elimination than because of the level attained, for this is in direct contrast to the curve for the normal individual. This test was performed 3 days after administration of cortin had been discontinued, but in order to eliminate this influence completely a second test was performed 3 weeks later resulting in chloride levels of 300 mg. and 367 mg. respectively per 100 cc. of urine. Although this was presumptive evidence that cortin had been responsible for the lower level of the first test, a third test gave values of 331 mg. and 335 mg. respectively during the course of cortin therapy (1 cc. twice daily). This response was probably due to the low dose employed.

On the basis of these findings a high salt intake with 1 cc. of cortin twice a day and 1 cc. of a pituitary extract twice a day was prescribed. This regimen was probably the most satisfactory from the standpoint of symptomatic improvement, but even this schedule failed to maintain the patient's general strength at a level commensurate with general activity. He continued to decline gradually with intermittent attacks of nausea and vomiting, weakness, prostration, anorexia and angina pectoris. In January, 1939, there was recession of the gingival margins to such an extent that his teeth began falling out. His paranoid ideas finally included not only his wife, but the family, hospital staff and attendants.

During the period of observation an effort was made to overcome the gonadal insufficiency by administration of a combination of gonadotropic preparations designed to stimulate testicular enlargement and secretory activity (pituitary gonadotropin[4] 1 cc., 20 R.U., plus 0.1 cc. of chorionic gonadotropin,[5] 10 R.U.). This combination was injected twice daily for 10 days. On the eighth day the patient demanded to know the nature of the injections because he had experienced erections for the first time in 5 years. When the treatment was explained, he requested that it be discontinued. The testes at this time measured 35 × 22 × 10 mm. and were normal in consistency. Within 10 days after cessation of the injections the testes were scarcely palpable as a soft doughy mass about 20 × 12 × 5 mm. Unfortunately biopsy material could not be obtained.

Although numerous blood counts were taken, the level of hemoglobin remained about 10 gm. per 100 cc. with the erythrocyte count approximately 3,700,000 in spite of various therapeutic measures. No definite reticulocyte response could be obtained with liver extract, iron, vitamin B_1, desiccated pituitary powder administered orally, and other measures. However, within 2 months after treatment was discontinued the hemoglobin level was 8.6 gm. and the erythrocyte count was 2,880,000. With the progressive reduction in hemoglobin and erythrocyte count to a level of 3.6 gm. and 1,300,000 cells, respectively, shortly before death; there were frequent attacks of angina pectoris, hypotension (80/50 to 90/60), intermittent episodes of stupor, progressive reduction in visual fields and finally death on July 26, 1939.

Necropsy was performed 2 hours after death. The important positive findings included the following.

The body of a fairly well-developed, poorly nourished elderly white man showed a peculiar waxlike pallor of the skin and practically complete absence of pubic and axillary hair. The serous cavities all contained some excess of clear fluid.

There was general atrophy of the organs, the following weights being recorded: heart 230 gm., spleen 115 gm., liver 910 gm., right kidney 84 gm., left kidney 95 gm. Although weights were not recorded, the adrenals, pancreas, prostate, testes and thyroid were considerably less than normal size and grossly were definitely atrophic. These findings were confirmed in each instance by microscopic examination.

A moderate degree of arteriosclerosis was seen in the aorta and some of its main branches, with consequent changes most evident in the scarred kidneys, atrophy and lipomatosis in the pancreas, and atheromatous ulcers in the abdominal aorta.

Cholecystectomy had been performed previously. Bilateral, partially calcified apical scars were seen in the lungs.

The examination of the brain revealed moderate changes associated with mild arteriosclerosis, confirmed by the microscopic examination.

The sella turcica was enlarged smoothly and eroded by an hypophyseal adenoma which measured 32 × 30 × 26 mm. This was encapsulated, and on section the tissue making it up bulged above the capsule and was fairly gelatinous and uniform. This tissue was reddish-brown, and there were thin white streaks of stroma through it, giving an irregular lobulation (fig. 1a).

Microscopic examination of the tumor revealed it to be made up of small cells with scanty chromophobe cytoplasm and oval vesicular nuclei. No mitotic figures were seen. The cells grew in comparatively large solid alveoli, which became linear in places. The stroma carried a copious blood supply, which in places opened out into broad blood lacunae (fig. 1b). At the border of this chromophobe adenoma of the hypophysis there was a thin layer of more normal anterior lobe tissue, which was compressed by the

[3] Antiutrin-G.
[4] Prephysin.
[5] Antuitrin-S.

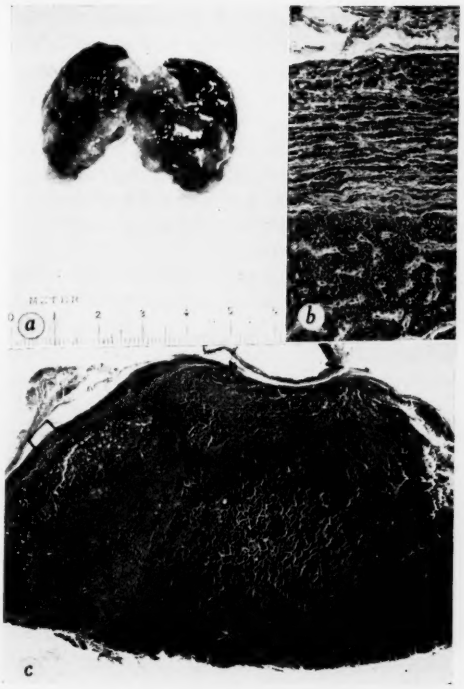

Fig. 1. (a) Gross section of the tumor, showing the dark portions which were reddish-brown and surrounded by the white strands of stroma cells. (b) A high power magnification of the thin strand of normal anterior lobe tissue taken from the square in (c). Note also the fairly large alveoli which are made up of solid chromophobe cells. (c) Low magnification of the entire tumor in cross section. Note the large blood lacunae near the center.

adenoma into long thin concentric alveoli against the capsule (fig. 1c). In these alveoli, eosinophilic, basophilic and chromophobic cells could be recognized.

A diagnosis of chromophobe adenoma of the hypophysis, with vestigial anterior lobe tissue was made.

Further microscopic findings were those of marked chronic atrophic gastritis with indifferent, intestinal type mucosa; heavy hemosiderin pigmentation of von Kupffer cells and liver cells, chiefly in the peripheral zone; some hemosiderin in renal tubular epithelium of the convoluted portion; and hemosiderin in phagocytes in the pulp of the spleen. The femoral bone marrow had been transformed to red marrow, and was of an hyperplastic, megaloblastic type. Hemosiderin in phagocytes was seen in this marrow. These findings contribute to a diagnosis of pernicious anemia.

Table 1. Chief Pathologic Findings

1. Chromophobe adenoma of hypophysis with Simmonds' disease
   a. Atrophy of thyroid, adrenals, pancreatic islands, prostate and testes
   b. General atrophy of muscles, skin and organs
2. Pernicious anemia
   a. Chronic atrophic gastritis
   b. Hemosiderin in liver, spleen and kidneys
   c. Hyperplastic, megaloblastic femoral bone marrow
3. Moderate arteriosclerosis
   a. Coronary
   b. Renal
   c. Cerebral
   d. Pancreatic
   e. Aortic
   f. Pulmonic

There was conspicuous eosinophilic infiltration in the lymphoid tissues of the body. This was seen in the tracheo-bronchial lymph nodes, spleen, mucosa of stomach, small intestine and colon.

The thyroid gland showed definite glandular atrophy and disappearance with progressive fibrosis. Little colloid was present in the remaining glandular alveoli.

The adrenals were very small in cross section, and the cortical atrophy was accompanied by fibrous thickening of the capsule. However, there was a moderate amount of lipoid in the remaining cortex, and an occasional small region of adenomatous hyperplasia was seen.

In the pancreas there was general parenchymal atrophy, and interacinar fibrosis, and the islands of Langerhans were small and atrophic. An occasional hypertrophic island was seen, but there were no acute degenerative changes.

Section of the rectus muscle revealed parenchymatous degeneration of the fibers, and some diffuse atrophy. Table 1 summarizes the chief pathologic findings.

In addition to the microscopic studies a bioassay of the pituitary tissue was performed to determine the presence of any of the various pituitary factors. The pituitary tissue was desiccated in acetone and powdered, yielding 800 mg. of finely screened powder from a half of the large adenoma. This powder was emulsified in physiologic saline solution and injected into 6, 21-day-old, rats over a period of 5 days. In doses ranging from 10 to 80 mg. of the powder there was no appreciable change in weight of adrenals thyroid, ovaries or uteri. To determine the presence of any augmenting substances follicle stimulating hormone (1 R.U.) and the adenoma powder (10 to 80 mg.) were injected simultaneously into another series of 6 immature rats. Instead of augmentation there was a slight reduction in average ovarian weight.

The bioassay for the melanophore principle was carried out by Dr. Graham Chen of the Department of Pharmacology, University of Chicago, using the hypophysectomized frog as test animal and the method of Teague (25). The adenoma contained about a twentieth as much of the melanophore principle as did normal human pituitary powder derived from a man aged 70 years who died suddenly of cerebral hemorrhage. A considerable amount of blood was present in the adenoma powder as a contaminant, a fact which accounts in part for the low concentration of melanophore principle.

The determinations of the pressor and oxytocic principles were undertaken by Dr. G. A. Fostvedt, Department of Pharmacology, University of Chicago. The assays were conducted on the cat for the pressor

activity and on the chicken for the oxytocic principle (16). Neither pressor nor oxytocic principle could be demonstrated in the adenoma. There was even a slight depressor substance of the blood or tissue extract, as demonstrated in the cat.

An assay for thyrotropic hormone using the day-old chick was carried out by Dr. R. F. Howe, Mayo Foundation, Rochester, Minnesota. Doses up to 10 mg. of dried powder in a group of 4 chicks failed to increase the weight of the thyroid gland or the height of glandular epithelium.

DISCUSSION

The essential features of pituitary deficiency disease have recently been well described by many authors (13, 18, 21) and the symptoms that are correlated with loss of gonadotropic, thyrotropic and growth hormones have been recognized (11, 26). The deficiency of adrenotropic activity has been suggested (19) but until Cutler's chloride excretion test was perfected no clue was available to demonstrate or measure this state of activity. Our limited experience suggests this test to be worthy of further trial in such cases. Attempts to differentiate anorexia nervosa by means of this test have been successful where the test has been properly executed (27), but in most instances in which the anorexia is of long standing this is impossible because of lack of cooperation by the patient. In one instance all the food and fluids prescribed for the first 24 hours were found hidden in the bed clothing. In two other cases vomiting was induced to relieve distention. Although the level of the urine was very high in these patients because of low urine output, the total excretion of chlorides was found to be within the normal range and the blood level was also found to be normal. Since this paper was prepared, Stephens (27a) reported chloride excretion levels of 6 cases having pituitary tumor (364 to 690 mg. of sodium chloride per 100 cc. of urine in the final specimen). This proves fairly conclusively the marked impairment of adrenocortical function in destructive lesions of the anterior pituitary.

In approaching the problem of pituitary deficiency disease one must keep in mind the various etiologic factors involved In destructive pituitary lesions. By far the greater number of cases reported to date (70%) result from atrophy and fibrosis of the gland. In such cases, the history of profound shock (postpartum hemorrhage, operation, trauma) is elicited in most instances (7, 14, 15, 17, 18, 28, 29).

Although pituitary tumors are relatively common, they are not frequently associated with deficiency states. This is probably due in part to the great margin of safety provided in pituitary function (30). In most instances the neurologic and visual complications incapacitate the patient before all functional elements of the gland have been destroyed. Of the various tumors involved, chromophobe adenomata and craniopharyngioma are most likely to produce this complex.

Pituitary deficiency states resulting from inflammatory conditions are quite rare (23, 31) and apparently only three of four cases of such states due to syphilis and a similar number of those due to tuberculosis have been reported.

The case here presented establishes a fact which is obvious from clinical study, namely that the chromophobe cells present in these large tumors are without endocrine function. They exhibit none of the common reactions of pituitary tissue except a possible inhibitory action on gonadotropic preparations. This also accounts for the absence of diabetes insipidus in the presence of a large tumor mass pressing on the hypothalamus, for as Ranson (32) pointed out there are two essentials for diabetes insipidus: a lesion of the posterior pituitary-hypothalamic system, and the metabolic (diuretic) activity of a normal anterior lobe of the pituitary.

The hemopoietic response in this case presents a more difficult problem. Stephens (18) has reported similar experiences in this type of anemia with liver extracts. We can only hypothesize that the nutritional and glandular factors responsible for the maintenance of hemopoiesis—even at a minimal level were indispensable and that their withdrawal precipitated a crisis which the bone marrow could not overcome. Many studies have been made in an attempt to establish the existence of a hemopoietic factor (33) of the pituitary, but the preponderance of evidence suggests that this function is mediated by way of the thyrotropic hormone (34).

SUMMARY

A verified case of Simmonds' disease in a white man, aged 62 years is reported. The patient's chief symptoms were bitemporal and bifrontal headaches (20 years), weakness and pains in the lower extremities (15 years), impotence and menopausal symptoms (6 years), episodes of nausea and vomiting with prostration simulating Addison's crises (6 years), and paranoid psychosis during the last 2 years.

The findings of note included pallor, loss of hair, atrophy of the genitalia and bitemporal quadrant defect in the field of vision. In addition to the usual findings of low basal metabolic rate, low blood sugar levels, and so forth, the patient exhibited a marked increase in chloride excretion suggesting impairment of adrenal function. This was borne out by his therapeutic response to high salt diet and cortin. His response to irradiation therapy was unsatisfactory.

Administration of growth hormone preparations resulted in marked improvement but this response was transitory. An interesting feature was the impairment of glucose absorption as evidenced by flat oral tolerance curves, whereas intravenous tolerance curves were essentially normal.

Another interesting finding was the presence of normochromic anemia associated with achlorhydria and cramplike pains of the lower extremities. Liver therapy failed to initiate a reticulocyte response, but following its withdrawal progressive anemia developed which terminated with a hemoglobin level of 5.0 gm. in 100 cc. of blood and an erythrocyte count of 1,400,000 in each cubic millimeter of blood.

Necropsy revealed a large chromophobe adenoma. Bioassay of 800 mg. of dried powder from this tumor failed to reveal evidence of activity except for small amounts of the melanophore principle.

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PITUITARY PATHOLOGY

VACUOLIZATION OF THE BASOPHIL CELLS OF THE PITUITARY BODY (PARS DISTALIS) IN RELATION TO AGE, MENSTRUATION, AND THYROIDISM

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THE PRESENT STUDY was undertaken primarily to determine whether or not there is any cyclic variation in vacuolization of the basophil cells of the pars distalis of the human pituitary body. The same cytoplasmic constituent was also considered in tissues from small groups of cases representing pregnancy, the menopause, senility and diseases of the thyroid gland. The study was entirely objective and, as far as the material permitted, quantitative.

As is the case with other cytologic details, most available references to vacuolization concern laboratory animals. Severinghaus' reviews of the literature (1, 2, 3) indicate that a persistent augmentation of vacuoles is associated with castration, hyperthyroidism and hypothyroidism. The basophil cells of castrated or thyroidectomized rats are greatly increased in number and contain prominent vacuoles, some of which are so large that a type of 'signet ring' cell, with nucleus and cytoplasm pushed to one side, is formed. Similar, but not so extreme, vacuolization occurs also in castrated or thyroidectomized rhesus monkeys. Hyperthyroidism, strangely enough, or the presence of the Walker sarcoma (4) produces in rats a moderate increase of vacuolization.

Data on human cases are not abundant. Biggart found in one man and three women castrated 2 to 6 years before death, that the basophil cells were increased and prominently vacuolated. Rasmussen and Severinghaus (2) have reported similar findings in the pituitary bodies of several women past 60, and the latter identified the change as one of physiological castration. The signet-ring cell does not develop in man. We have found no observations in the literature in human cases of hypo- or hyperthyroidism. Eisenhardt (5) reported slight but conspicuous vacuolization of basophil cells in the pituitary bodies of patients with diabetes mellitus. In pituitary basophilism there is not only the hyaline change of Crooke, but also other changes of the cytoplasm of basophil cells, including excessive vacuolization (6).

The significance of the vacuoles is open to question. Although some (7, 8) interpreted the many large vacuoles due to castration as evidence of increased activity, others (2, 9) consider them evidence of degeneration. The suggestion (8) that small droplets within the Golgi apparatus unite to form the large vacuoles has been rejected (2) on the ground that vacuoles may be found entirely apart from the Golgi apparatus, and are often stainable, unlike the Golgi droplets. There is a report (10) tending to demonstrate the formation of both staining and non-staining vacuoles through the clumping together and ensuing liquefaction of the basophil granules.

Severinghaus' scheme of endocrine activity (10) conceives that the secretions of the pituitary body and of the "end" organs (gonads, thyroid, adrenals) are mutually stimulating, so that inhibition at one end, such as by castration or thyroidectomy, will cause degenerative changes at the other, namely the pituitary body, and vice versa. According to this theory vacuolization is simply one evidence of degeneration.

MATERIALS AND METHODS

The material for the present study consisted of stained sections of the pituitary body in 81 cases. Fifty-four were from women, normal as far as the reproductive system was concerned, 42 actively menstruating, 6 in the menopause, and 6 senile (table 1). In the normally menstruating group the day of the cycle on which the patient died was known either exactly or within a range of 2 days. There were also available 10 cases of thyroidism, 10 of pregnancy, and 7 of castration (table 2).

The tissues were obtained in the course of routine necropsies in which permission to examine the brain had been granted. Each pituitary body had been removed by breaking off the posterior clinoid processes with bone forceps and removing the body surrounded by its fibrous coat. It was then placed in a 10% solution of formalin and stored. The specimens of the present study were selected from a large number of pituitary bodies which had been preserved under the direction of Dr. J. W. Kernohan of the Mayo Clinic who kindly made the material available.

In preparing the sections, the bodies were removed from the formalin and cut into sections paralleling the longest axis of the gland. Some of these blocks were then placed in Zenker's fluid for 24 hours, while others were placed in Weigert's first and second

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TABLE 1. VACUOLIZATION OF BASOPHIL CELLS IN NORMAL WOMEN

Case No.	Age	Day of cycle	Cells counted	Unweighted index	Weighted index
1	16	9	230	.23	.11
2	18	14	249	.62	.44
3	19	12	245	.37	.25
4	20	8	204	.61	.39
5	22	16	227	.70	.47
6	22	21	207	.38	.20
7	22	27	200	1.11	.67
8	23	20	206	.84	.52
9	24	14	203	.94	.52
10	27	24	205	.45	.30
11	28	17	202	.88	.51
12	28	19	232	.87	.59
13	29	17	232	.62	.43
14	29	14	202	1.00	.69
15	31	7	200	1.58	1.43
16	31	11	207	.78	.40
17	32	17	237	.45	.33
18	33	9	203	1.48	.99
19	33	18	205	1.12	.88
20	34	14	219	1.25	.80
21	35	17	235	.85	.61
22	35	19	224	.64	.34
23	35	22	200	1.01	.74
24	35	23	208	.85	.57
25	35	25	227	1.32	.97
26	36	16	204	1.15	.68
27	37	14	204	.83	.61
28	37	15	219	.78	.63
29	37	27	222	1.01	.68
30	38	23	208	1.45	1.20
31	39	27	203	1.74	1.52
32	39	28	205	.97	.64
33	41	16	205	.84	.52
34	41	28	203	.97	.39
35	44	5	219	.88	1.02
36	46	3	214	1.53	1.01
37	47	16	207	1.21	.90
38	47	23	217	.75	.55
39	48	17	205	1.04	.77
40	49	15	206	.84	.56
41	32	*	208	.93	.49
42	41	*	220	.53	.36
43	48		204	1.60	1.06
44	46		202	2.45	1.42
45	55		201	2.30	1.68
46	53		207	1.77	1.33
47	51		204	2.24	1.46
48	51		202	1.70	1.11
49	48		201	.87	.50
50	63		201	1.10	.63
51	77		200	1.72	1.15
52	83		205	1.92	1.36
53	54		200	1.51	.99
54	73		203	2.58	2.12

* See discussion.

mordants. After dehydration, they were embedded in paraffin in the usual manner. Sections, 5 microns thick, were cut from these blocks and were stained by the modification of Mallory's acid fuchsin aniline-blue method which was recommended by Crooke (11). With this stain the cytoplasm of the chromophobe cells either does not stain at all or is pale blue; the eosinophil granules stain bright red and the basophil granules stain dark blue, whereas the hyaline substance of Crooke stains uniformly pale blue.

In pituitary tissues which have been in formalin for many years before being cut and embedded, the granules of the basophil cells do not stain clearly. Accordingly, there were excluded from this study all pituitary bodies which had remained in formalin too long.

All the slides were examined at 570 diameters with the aid of immersion oil. To make our figures objective, the microscopic study was made without reference to clinical data. Correlations between histologic and clinical data were attempted only after completion of the observations. The vacuoles of at least 200 basophil cells were counted in each case. Results in each slide were first determined for separate groups of approximately 100 cells in different parts of the pars distalis, one group usually from the periphery of a given section and the other from the central portion. The purpose of the sub-determinations was to check on the consistency of vacuolization for the specimen in general. It was found that, for all the slides, the difference between the two sub-groups averaged 29% of the result for the slide; or, in other words, counting 100 cells would have been 14.5% less accurate than counting 200 cells. The rows in which the cells were counted varied in width according to the abundance of basophils, but within each row every basophil which included a nucleus was tabulated. Because of apparently transitional forms, there was frequent difficulty in distinguishing basophil from chromophobe cells. As a general criterion, every cell with clearly defined blue granules was considered a baso-

TABLE 2. VACUOLIZATION OF BASOPHIL CELLS IN THYROIDISM, PREGNANCY AND AFTER OVARIECTOMY

Case No.	Age	Clinical data	Cells counted	Unweighted index	Weighted index
55	35	Exophthalmic goiter (male)	204	.60	.40
56	53	Exophthalmic goiter	201	1.80	1.24
57	62	Exophthalmic goiter	208	1.56	1.38
58	54	Exophthalmic goiter	209	1.73	1.27
59	76	Exophthalmic goiter (male)	210	.81	.57
60	49	Adenomatous goiter	201	1.47	.83
61	72	Adenomatous goiter	204	1.82	1.24
62	66	Myxedema, originally exophthalmic goiter	204	1.29	.96
63	71	Myxedema	204	1.81	1.84
64	48	Myxedema (male)	204	1.02	.62
65	37	Last menstrual period 16½ mo. previous at onset of pregnancy	200	1.45	.89
66	24	Pregnant 4 mo.	202	1.37	.54
67	32	8 weeks postpartum	205	.90	.38
68	24	5 weeks postpartum	203	.56	.24
69	25	6 mo. postpartum, but with one period 5 mo. previously	201	.57	.22
70	30	5 mo. postpartum, but with one period 2 mo. previously	206	1.09	.73
71	21	Pregnant 3 mo.	201	.28	.14
72	27	3 mo. postpartum	201	1.13	.52
73	25	3 mo. postpartum	203	.73	.37
74	27	6 weeks postpartum	200	.77	.39
75	34	Ovariectomy 8 days previously	203	1.46	.85
76	38	Ovariectomy 16 days previously	200	1.14	.77
77	41	Ovariectomy 20 yr. previously	202	1.93	1.28
78	43	Castration by x-ray 12 mo. previously	206	3.80	1.82
79	34	No menses for 16 mo. because of chronic pulmonary tuberculosis	202	1.46	.77
80	37	Partial resection 12 yr. previously but regular periods continuing	200	1.39	.80
81	20	See discussion	202	.95	.52

phil, unless the visible area of cytoplasm was smaller than the nucleus, or the staining was considerably lighter than in other basophil cells of the same slide.

Two figures were determined for each slide—an "unweighted" and a "weighted" index. The "unweighted" figure is the average number of vacuoles per basophil cell, regardless of size. The "weighted" figures attempt to compare average vacuole area per cell. To this end, each vacuole was scored as follows. Those with diameter less than 1.7μ counted as 1/3 or ¼, depending upon convenience in adding; those between 1.7 and 3.4μ counted as ½; those between 3.4 and 5.2μ counted as 1; those between 5.2 and 6.9μ counted as 2, and those above 6.9μ (only 0.59% of the total) counted as 3. No distinction was made between staining and non-staining vacuoles.

RESULTS

The 42 slides from the actively menstruating patients (*cases 1–42*, table 1) were examined in order to study two possible relationships: (*a*) between vacuolization and day of the cycle; (*b*) between vacuolization and age. They also were to serve as controls for other studies. *Cases 41* and *42*, which are included in this series, involve special conditions. In *case 41* there was amenorrhea until one month before death, and in *case 42* the last menstrual period continued 2 months, stopping 7 days before death. When all data in the group were assembled and graphed, it was found that there is no correlation whatever between vacuolization and day of the cycle, but that a rising curve is evident in the plotting of vacuolization against age. This curve rises sharply between ages 16 (the youngest in our series) and 35, from which point it tends to rise less steeply. It is noteworthy that the observations from the 10 pregnancy cases (*cases 65* to *74*, table 2) when superimposed on this graph, reinforce the trend for the normally menstruating group. Since it is already established that vacuolization is more marked in the aged than in young persons (2, 7, 12), the similar tendency for vacuolization to increase steadily during the fertile period is an interesting and consistent observation. Indeed, after all the cases were tabulated, it was seen that most of the vacuolization seems to occur before the menopause.

In table 1 is also a control series of 6 cases in the menopause (*cases 43–48*) and 6 in old age (*cases 49–54*). Indices of vacuolization in these groups are high.

Ten cases of disease of the thyroid gland are represented in *cases 55–64* (table 2). *Cases 55* to *60* were instances of hyperthyroidism and *62* to *64*, hypothyroidism. In *case 61* the adenomatous goiter was not associated with other symptoms. *Cases 55*, *59* and *64* were the only tissues from males in the present study. The indices for the thyroid group are high, but they are not higher than the control indices for corresponding ages.

The ten pregnancy and postpartum cases (*65–74*, table 2) have indices no different from those of corresponding ages in the control series (table 1). Incidentally, vacuolization was not mentioned in the literature among the changes in the pituitary bodies of pregnant laboratory animals.

Tissues from only 7 cases following ovariectomy were available (*75–81*, table 4). In one of these, *case 80*, the patient had had monthly 'spotting,' had received anterior pituitary-like hormone[1] and theelin for 18 months prior to death, and died of a brain tumor. The weighted indices of vacuolization tend to be slightly higher than the average for the corresponding age groups, and very high in the 2 cases (*77* and *78*) in which the castration was of long standing. Although there is a suggestion that castration increases vacuolization, the number of cases in this group is too small to warrant any conclusions.

SUMMARY

The extent of vacuolization of the basophil cells of the pars distalis of the pituitary body was determined quantitatively in 81 cases, 78 female and 3 male. The tissues were from 54 patients either normally menstruating, in the menopause, or senile, and 27 who had disease of the thyroid gland, were recently pregnant, or had been castrated. The day of the cycle on which the patient died was known for 40 cases with normal menstruation. All the microscopic observations were made before comparing the results with the clinical data.

There was found no cyclic variation of vacuolization of the basophil cells in relation to menstruation. However, vacuolization increased gradually with age before, during, and after the menopause. The degree of vacuolization during and after pregnancy conforms to that expected for the patient's age. The results for thyroidism and castration are recorded but are inconclusive, because of the small number of such cases in our series.

It is with pleasure that I acknowledge the assistance of David Haft in the microscopic studies here presented.

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[1] Antituitrin-S.

ACROMEGALY

THE THYROID GLAND IN 166 CASES OF ACROMEGALY[1]

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IT IS A FACT that the thyroid gland frequently is enlarged and the basal metabolic rate is elevated in the presence of acromegaly. In 1897, Magnus-Levy (1) described a case in which there was a continuous elevation of the rate of consumption of oxygen similar to the elevation found in Basedow's disease. He also called attention to certain symptoms which occurred inconstantly in association with acromegaly and which resembled those of Basedow's disease.

In 1922, Boothby and Sandiford (2) found the basal metabolic rate greater than +10 in 50% of a series of 30 cases of acromegaly. Cushing and Davidoff (3), in 1927, found the B.M.R. to be greater than normal in 49 of a group of 72 cases of acromegaly. The average was +18.6. In the remaining 23 cases, the B.M.R. was less than normal, averaging −8.3. Davidoff (4) also found some degree of enlargement of the thyroid gland on physical examination in 25 of 100 cases of acromegaly.

The discovery of the thyroid-stimulating effect of preparations of the anterior lobe of the pituitary gland and the isolation of this thyrotropic substance in a highly purified form by Anderson and Collip (5) established a rational explanation of the behavior of the thyroid gland in the presence of acromegaly.

As a basis for this presentation, the physical findings of the thyroid gland and the basal metabolic rates in the cases of acromegaly which have been observed at the Mayo Clinic were reviewed. The records of 271 cases in which the diagnosis of acromegaly had been made, either tentatively or unqualifiedly, were studied. The records of 166 cases were selected as a basis for this report; 105 were not included either because the diagnosis was not sufficiently well established or because adequate data were not recorded.

The principal requirements for inclusion in the series were that the patient have the characteristic appearance of acromegaly, with enlargement of the acral parts and maxillary prognathism. These characteristics were present in all cases. Eighty-seven patients were females and 79 males. A definite history of the time of occurrence of the acromegalic changes was obtained in 132 cases. In 148 cases roentgenologic examination of the skull revealed enlargement and erosion of the sella turcica. In 17 cases, roentgenologic evidence of change in the sella turcica was absent or questionable. Roentgenologic examination was not obtained in one case. The enlargement of the sella was graded 2+ or more on the basis of 1 to 4 in 104 cases.

The thyroid gland was described as enlarged in 86 of the 166 cases; in 80 cases, the findings were recorded as normal or were not described. The latter was accepted as evidence that the gland was not enlarged. The thyroid contained adenomas in 53 of the 86 cases in which it was enlarged. It was palpable in 24 cases and in 2 cases diffuse colloid goiter was found. The thyroid gland was described only as "enlarged" in 7 cases. The adenomas varied in size from small nodules to very large tumors that caused tracheal compression.

The basal metabolic rate was determined once or more than once in 135 of the 166 cases. It was higher than normal in 116 cases, the average of these being +18.3. It was below normal in 17 cases and in these the average was −6.9. In two cases the rate was ±0. The average B.M.R. for the entire group of 135 cases was +14.7.

The distribution of the basal metabolic rates and their relationship to the physical findings in the thyroid gland are shown in table 1. It is seen that for the entire series and for each of the subgroupings, according to the condition of the thyroid gland, the B.M.R. was greater than normal. The values in 52% of the cases were greater than +10 as contrasted with the fact that only 8% of normal individuals have basal rates of more than +10. The group of cases in which the thyroid contained definite adenomas comprised the cases in which there was the greatest increase (mean B.M.R. +24.2; in 75% of the cases, more than +10). The group of cases in which the thyroid was palpable was next (mean, +11.0; in 43% of the cases, more than +10). The group in which the thyroid gland was not palpable was that in which the lowest rates were obtained (mean, +9.6; 39% of the cases, more than +10).

It is of interest to note that while the basal metabolic rates were very definitely elevated in some cases, in others they were normal or less than normal. This

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TABLE 1. BASAL METABOLISM IN ACROMEGALY

B.M.R.	Thyroid Gland							
	Not palpable		Palpable		Adenoma		Total	
	No. cases	%	No. cases	%	No. cases	%	No. cases	%
−30 to −21			1	3.3			1	0.7
−20 to −11	3	5.3			1	2.1	4	3.0
−10 to − 1	6	10.5	5	16.7	1	2.1	12	8.9
0 to + 9	26	45.6	11	36.7	10	20.7	47	34.9
+10 to +19	11	19.3	5	16.7	11	22.9	27	20.0
+20 to +29	8	14.0	4	13.3	11	22.9	23	17.0
+30 to +39	2	3.5	3	10.0	6	12.5	11	8.1
+40 to +49			1	3.3	3	6.3	4	3.0
+50 to +59	1	1.8					1	0.7
+60 to +69					3	6.3	3	2.2
+70 to +79					2	4.2	2	1.5
Total	57	100	30	100	48	100	135	100
Mean B.M.R.	+9.6		+11.0		+24.2		+14.7	
B.M.R. +10 or more, percentage of cases	38.6		43.3		75		52.5	

marked variation in the individual case may be explained by the assumption that the excessive production of hormone by the anterior pituitary lobe is not necessarily a continuous and permanent affair, but that there may be exacerbations and remissions of secretory activity so that the diagnostic evidences of acromegaly may not indicate overactivity of the anterior lobe at the time of observation but may only mean that this hyperactivity has occurred in the past.

An alternative explanation is that all components of the hormone of the anterior pituitary lobe may not be produced to the same degree in the presence of acromegaly and thus there may be an overproduction of the growth hormone and not of the thyrotropic substance.

Unfortunately, there is no simple method of determining the degree of activity of the anterior lobe at any particular time and of determining whether or not it parallels the basal metabolic rate.

Resection of the thyroid gland was performed in 27 cases and in one of these a second resection was performed, 5 years after the first operation, for recurrence of the goiter. Resection of the thyroid was advised in these 27 cases for one or more of the following reasons: obstructive dyspnea, in 7 cases; clinical evidence of hyperthyroidism, in 24 cases; and hypertensive heart disease in association with clinical evidence of hyperthyroidism, in 5 cases.

Five patients died following operation. In 2 cases the cause of death was pneumonia and tracheotomy had been necessary following thyroidectomy. These two deaths occurred previous to the advent of oxygen therapy. The third patient died in diabetic coma in spite of receiving what at that time was considered to be very large doses of insulin. The fourth patient died in acute delirium which seemed to be the result of the intracranial lesion and not of acute hyperthyroidism. One patient died with marked febrile reaction, with hemorrhagic edema of the lungs.

The basal metabolic rate was determined in each of the 27 cases previous to resection of the thyroid gland. It ranged from +1 to +75 with an average of 29.9. Seven of the cases had a partial thyroidectomy; the weight of thyroid tissue removed varied from 15 to 470 gm. with an average of 159 gm. In 26 cases, adenomas were present in the removed thyroid tissue. In 23 cases, the adenomas were in colloid thyroid glands, in 3 cases the adenomas were in a hypertrophic parenchymatous thyroid gland characteristic of exophthalmic goiter and in one case the removed tissue proved to be colloid thyroid gland, only.

The 3 patients who had parenchymatous hypertrophic thyroid glands received compound solution of iodine; 2 patients received it previous to operation and the other patient received it 2 years later when the disease in mild form recurred. There was no appreciable change in the B.M.R. of the 2 patients who received iodine previous to operation, although one patient gained 16 pounds (7.3 kg.) in 26 days. The other patient who experienced recurrence of the disease following thyroidectomy improved following the administration of iodine and the B.M.R. fell from +20 to +12.

Basal metabolic rates were obtained in 16 cases of acromegaly following resection of the thyroid (table 2). In the last 2 cases, the determinations were unsatisfactory as the patients had congestive heart failure, when the studies of metabolism were performed.

Basal metabolic rates were obtained in 12 cases during the first month subsequent to operation. In 10

cases the rate was lower than the preoperative level. In 2 cases there was no change. The decrease ranged from 2 to 53 points, with an average of 13 points.

In contrast with these data is the observation of Cushing and Davidoff (3) that operations on the chromophilic hypophysial adenoma itself in cases of acromegaly were followed by a fall in the B.M.R. which was almost as uniform and as striking as the effect following operations on the thyroid gland in cases of exophthalmic goiter. Seventeen patients having acromegaly, whose average preoperative basal metabolic rate was +10, had an average rate of −7 subsequent to operation.

It might be anticipated, in accordance with the findings of Marine and Rosen (6) which have been corroborated, that an increasing exophthalmos might follow resection of the thyroid gland in the presence of acromegaly. A certain number of these patients, at least, must have had a persistently increased amount of thyrotropic hormone. Although this possibility was not in mind during the postoperative period of observation of the patient, no instances were recorded in which the appearance of exophthalmos or its increase, if it was already present, was noted.

Persistent hyperthyroidism tends to lead eventually to myocardial insufficiency and it would be anticipated on that basis alone that the tendency would be apparent in the presence of acromegaly. We have not had the opportunity to follow many of our cases over any very prolonged period of time, but we have been impressed by this tendency. Recently, Courville and Mason (7) reported 24 cases of acromegaly. In 6 the cause of death was cardiac failure and in 18 there was some evidence of cardiac failure. However, they concluded that the principal factors in the production of myocardial insufficiency in acromegaly were the increased "work demand" occasioned by the splanchnomegaly, and the overgrowth of the heart itself, stimulated as other viscera are by the influence of the pituitary hormone. They also found that an elevated B.M.R was not a constant factor in cases of acromegaly in which the patient had cardiac failure.

One of the cases in which thyroidectomy was performed is of sufficient interest to warrant a somewhat detailed report, because the response was exceptional and because the opportunity for observation over a period of 18 years was afforded.

CASE REPORT

The patient, an unmarried, white woman, was 31 years of age when she registered at the clinic on Jan. 12, 1921. Her chief complaints at that time were nervousness, headaches and pruritus. She stated that she had had good health until 6 years previously. At that time, she had experienced periods of depression but she remained active for 2 years, when the depression became so severe that she became completely disabled. She also noted the presence of a goiter at that time, the menses ceased for 18 months, and she began to have periods of swelling of her face and hands, of short duration. There was pain in the hands and blanching and numbness of the fingers of the right hand. Her features became coarse, the nose large and the lips thick. The voice became coarse. The glove size increased from 5½ to 7, the shoe size from 2½ to 3½, and the patient's weight increased from 115 lb. (52.2 kg.) to 127 lb. (57.8 kg.). Six months before her registration at the clinic, she had had headaches of 3 days' duration and one month previous to her examination here, she had had an attack of headache of 8 days d[illegible]ation in the course of which she had vomited several

TABLE 2. THE BASAL METABOLIC RATES IN SIXTEEN CASES OF ACROMEGALY FOLLOWING RESECTION OF THE THYROID GLAND

Case	Ave. B.M.R. before operation	Basal metabolic rates: Time after operation: Weeks 1	2	2½	3	Months 1	3	6	16	Years 2	3	6	10	18	Pathology	Wt. of thyroid tissue removed gm.	Thyroidectomy
1	+72	+34	+19					0			+4	+4		+24	A[1]	70	+
2	+32				+18										A	242	+
3	+33			+16	+18										A	371	+
4	+ 7							−1	−4						A	20	+
5	+25	+35		+15											A	120	+
6	+43		+27				+34			+14			−19		A	302	+
7	+29					+24									A	50	+
8	+17	+16			+15										A	390	+
9	+ 9					+9									A	204	+
10	+10.5		+11												A	70	+
11	+40								+32[2]						A	82	Partial
12	+18			+14	+27										A	470	Partial
13	+42			+27						+22					PH[3]	84	+
14	+28		+28			+17									PH	15	Partial
15	+66		+66				+55[4]								A	17	Partial
16	+23								+58[4]						A	66	Partial

[1] Adenoma in colloid thyroid.
[2] Rate obtained elsewhere.
[3] Diffuse parenchymatous hypertrophy.
[4] Myocardial insufficiency.

times. She had noted excessive perspiration for 3 years. Seven months previous to examination here, the intermenstrual period had increased from 4 to 6 weeks. She had a tremor of the hands for 8 months and weakness of the legs for 4 months. She was very intolerant to heat and had a very good appetite.

At the time of the physical examination, the patient's weight was 115½ lb. (52.3 kg.). The features were noted as large and the hands were described as "spade-like" with pudgy fingers. The skin was warm and moist and there was a definite tremor. There was a tumor of the thyroid gland 2 by 2½ in. (5 by 6.25 cm.) in size. The specific gravity of the urine was 1.018 and there was no glycosuria. The Wassermann test gave negative results. Laryngoscopic examination did not reveal laryngeal changes characteristic of acromegaly.

Roentgenologic examinations of the hands, feet and mandible gave negative results. Roentgenologic examination of the head revealed enlargement of the sella turcica with erosion of the posterior clinoid processes. Examination of the ocular fundi gave negative results and the fields were normal on rough test. Twelve determinations of basal metabolic rate were made; the average value was +71.

A diagnosis of pituitary tumor with acromegaly and adenomatous goiter with hyperthyroidism was made. On Feb. 1, 1921, thyroidectomy was performed. The adenoma was extirpated together with a portion of the right lobe, the isthmus, and a portion of the left lobe which was about normal in size. The surgeon estimated that he had preserved glandular tissue equivalent to that of a lobe of normal size on the right and half of such on the left. The adenoma measured 6 to 7 cm. in diameter and the weight of the removed thyroid tissue was 70 mg. Microscopic examination revealed multiple, hemorrhagic, degenerating hyaline-fibrous, colloid and fetal adenomas with moderate parenchymatous hypertrophy, intra-adenomatous.

Convalescence was satisfactory. The six basal metabolic rates obtained indicated that the rate decreased steadily from +93 on the third postoperative day to +19 at the time of dismissal on the fifteenth postoperative day.

We examined the patient again 4 months following operation. She had gained 10 lb. (4.6 kg.), her strength had improved and the menses were regular, but she continued to have spells of depression. Perimetric fields were obtained on the occasion of this visit, and they were normal. The B.M.R. was ±0.

The patient was next seen in April, 1924, 3 years after operation. Her complaints at that time were numbness of the fingers, nervousness and recurrence of the enlargement of the thyroid. Her weight was 125 lb. (56.7 kg.). There had been no increase in the size of the hands or of the face. The menses were regular but had been absent for 18 months after her last visit. There was an adenoma measuring 1 inch (2.5 cm.) in diameter in the left lobe of the thyroid. The B.M.R. was +4.

The patient's next visit to the clinic was in June, 1927. She returned at this time because of further enlargement of the thyroid gland and because the fingers had been enlarging further in the preceding 6 months.

Her weight was 123 lb. (55.9 kg.). There was adenomatous enlargement of the thyroid that involved both lobes. The menses were regular. Perimetric fields were normal and the basal metabolic rates obtained at this time were +4 and +2.

The patient next returned to the clinic in July, 1938. Her weight was 119 lb. (54 kg.). The menses had ceased 3 years previously, at the age of 46 years. The bilateral enlargement of the thyroid was practically unchanged from that of the previous visit. There had been some separation of the lower incisors during the previous 2 years. The perimetric fields were normal and funduscopic examination gave negative results. The basal metabolic rates were +31 and +21. Roentgen therapy over the region of the pituitary gland was administered.

In September, 1938, the patient returned: her B.M.R. was +24. The patient's final visit to the clinic was in January, 1939, and at this time the basal metabolic rate was +21. Relatives reported that the patient died in coma on July 14, 1939.

Roentgenologic examination of the skull of this patient at three different times showed enlargement of the sella turcica with thickening of the skull. There was some prognathism. The outline of the sella turcica showed both an increase in size and change in contour in the third film obtained as compared with the first two roentgenograms, and there also appeared to be further increase in the thickening of the skull in the third film.

There was recurrence of the goiter and what is more unusual, recurrence of hyperthyroidism. In our experience, it is extremely rare for hyperthyroidism to develop in association with recurrence of adenomatous goiter. The development of the hyperthyroidism, in itself, in this case suggests an unusual stimulation of the thyroid.

That the course of the acromegaly was of 25 years' duration and that the patient experienced a fair degree of health during that time argue for the mildness of the hyperpituitarism. Although this is an isolated case, it does indicate that it is possible to obtain satisfactory results following thyroidectomy for adenomatous goiter with hyperthyroidism in the presence of acromegaly.

SUMMARY

The records of 166 cases of acromegaly form the basis of this report. The condition of the thyroid glands and the basal metabolic rates in these cases were noted.

In accordance with the findings obtained from previous studies, the thyroid is frequently enlarged in the presence of acromegaly. In this series, it was enlarged in approximately 50% of the cases.

Also, in accordance with previous investigations, the basal metabolic rate often, although by no means

always, is elevated. The general average B.M.R. in the cases which we studied was +14.7.

In those cases in which distinct adenomatous enlargement of the thyroid was present, there was a tendency for the B.M.R. to be higher than it was in the cases in which adenomas in the thyroid could not be definitely palpated.

Thyroidectomy in the presence of acromegaly is associated with a high surgical risk.

Thryoidectomy for hyperthyroidism in association with acromegaly usually results in some fall in the B.M.R., but this is much less consistent and much less in degree than is the drop in rate which follows thyroidectomy for hyperthyroidism which is not associated with acromegaly.

Histologic examination of the thyroid tissue removed at the time of resection revealed the presence of adenomas in colloid thyroid tissue in 23 cases, adenomas in hypertrophic parenchymatous thyroid tissue in 3 cases and colloid thyroid tissue, only, in one case.

One case is reported in detail in which thyroidectomy for hyperfunctioning adenomatous goiter associated with acromegaly was followed by a prompt fall in the basal metabolic rate to normal. There was a recurrence of the adenoma and eventually a recurrent elevation of the basal metabolic rate years later.

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HYPOTHYROIDISM

HYPERCHOLESTEROLEMIA

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IT IS WELL KNOWN that hypercholesterolemia is an almost invariable finding in either spontaneous or postoperative myxedema. This has been confirmed from numerous sources (1, 2). It may also be found in other disorders, and at times in apparently normal individuals. It is, therefore, not pathognomonic of thyroid deficiency. Likewise, no other single physical abnormality, symptom or other laboratory finding is in itself diagnostic of myxedema. Hypercholesterolemia is as consistent an abnormality as any found in this disorder, and therefore deserves its share of importance in the diagnostic survey.

Experience has demonstrated that it is safe to conclude that a level of 300 mg. of cholesterol per 100 cc. of blood is well above the average normal value, which is approximately 180 mg. per 100 cc. We have shown diagrammatically in figure 1 what we believe is a reasonable scale of normal values. With this in mind, we felt that valuable information might be obtained by studying all case records in which a blood cholesterol value of over 300 mg. was found. In a 7-year period from Jan. 1, 1932, to Dec. 31, 1938, 404 such individuals were seen at the Lahey Clinic.

The reasons for blood cholesterol determinations in these patients varied. Myxedema was obviously present in many; in others a question of myxedema may have been raised. Blood cholesterol determinations were made in nearly all cases of pituitary tumor, xanthelasma, nephrosis, and jaundice seen personally by one of us. Many were taken routinely during a study of several hundred cases of nontoxic goiter, a group in which various other lesions were found.

While it would be desirable to study the entire group of patients in whom cholesterol determinations were made, we were primarily interested in determining what the probable chance was of hypercholesterolemia being due to myxedema, and hence the relative value of this test as an aid in making that diagnosis.

We realize that the normal frequency curve of blood cholesterol must vary, as do most biological measurements, and that it is perfectly possible for myxedema to exist with cholesterol levels in the normal range, but if hypercholesterolemia is a fairly constant feature of myxedema, a more reasonable conclusion as regards its value might be reached by an analysis of cases in which values within the probable normal range could be excluded. Of the 404 cases, the majority had a value below 500 mg., and in only 4 cases was it above 700 mg. Table 1 shows the diagnosis in the various groups. Sixty-four per cent of all the cases were thought to be examples of thyroid deficiency.

There were 93 cases of spontaneous or idiopathic myxedema, including all age groups. These consisted almost entirely of untreated cases, or a few cases in which desiccated thyroid was temporarily withdrawn. This number represents an incidence of 0.13% of the total new patients admitted to the clinic in this 7-year period. Estimates of the incidence of myxedema from several sources vary from 0.01 to 0.08% (3). The exclusion from this group of cases of myxedema with a blood cholesterol of under 300 mg. would not raise the incidence of myxedema to more than 0.15% at the most.

The 124 known cases of postoperative myxedema with cholesterol values of 300 mg. or over represent 1.4% of 8,524 thyroid cases of all types in which operation was performed during this interval. The cases of transient postoperative hypercholesterolemia are examples of those individuals who, shortly after operation, exhibit a definitely low metabolic rate, an elevated cholesterol level, frequently a degree of mental sluggishness and undue sensitivity to cold, but who ordinarily recover promptly, usually without requiring thyroid medication.

Of the 5 patients with pituitary disease, 3 had chromophobe adenomas, one was an acromegalic and one a pituitary dwarf. Cholesterol determinations were made in 30 cases of chromophobe adenoma, but only 3 showed hypercholesterolemia (*i.e.* over 300 mg.).

Eleven cases of xanthelasma fell in this group. The possible relationship between this condition and hypercholesterolemia has been studied before. Our in-

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TABLE 1. TYPES OF THYROID CASES WITH HYPERCHOLESTEROLEMIA SHOWING DISTRIBUTION AND PERCENTAGE

	Number of cases	Percentage
Total number (thyroid and nonthyroid)	404	
Spontaneous myxedema	93	23
Postoperative myxedema	124	30
After total thyroidectomy for heart disease	13	3
Transient hypercholesterolemia following thyroid operations	34	8

TABLE 2. NONTHYROID CASES WITH HYPERCHOLESTEROLEMIA SHOWING DISTRIBUTION AND PERCENTAGE

	Number of cases	Percentage
Pituitary disease	5	1.0
Diabetes mellitus	18	4.5
Xanthelasma	11	3.0
Liver and biliary tract disease	18	4.5
Renal disease	5	1.0
Coronary disease and angina pectoris	14	3.0
Obesity	23	6.0
Hypertension and/or arteriosclerosis	9	2.0
Miscellaneous	42	11.0

on one eyelid disappeared and that on the other lid became smaller. The blood cholesterol had undergone no significant change.

In regard to the patients with diabetes, it has been thought that only those with uncontrolled diabetes at the time the test was made showed hypercholesterolemia of this degree. This impression, however, was not always found to be true.

No conclusion can be drawn from the small number of cases of cardiovascular diseases, but Blumgart (4) found in general average values in these cases. As might be expected, hypercholesterolemia was found in cases of liver and biliary tract disease, especially in obstructive jaundice. The value of this test in the differential diagnosis of jaundice is frequently overlooked.

In 42 instances, no organic disease was found; in many of these cases purely functional disorders were present. In some of these cases blood cholesterol values as high as 400 mg. were found, with or without low metabolic rates. Desiccated thyroid was given at times especially when a low metabolic rate was found,

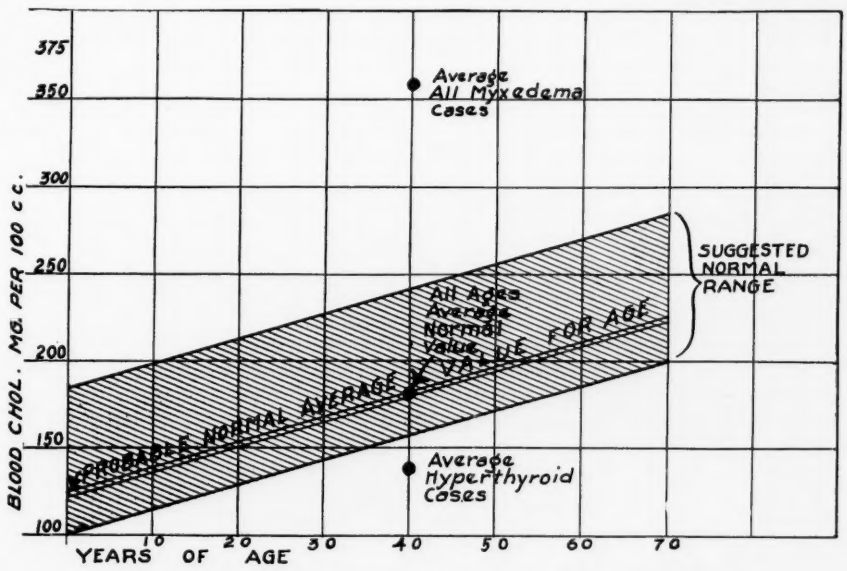

Fig. 1. RANGE OF PROBABLE NORMAL VALUES OF BLOOD CHOLESTEROL AT VARIOUS AGES.

terest in this question was aroused by the statement of a physician's wife who claimed that during the eight or ten years in which she had suffered from hyperthyroidism the lesions had disappeared from her eyelids; they began to return a year or so following subtotal thyroidectomy. Another patient with xanthelasma was placed on a low cholesterol diet and to our surprise returned 4 years later having religiously adhered to it. During that time a small lesion even though diagnosis of myxedema could not possibly be made from the history or physical examination. Little or no improvement followed in most instances. As was pointed out before, when physical signs are equivocal there may be a few surprises when thyroid is given in the usual doses (1 to 3 grains). Unless this response is accompanied by the prompt (3 to 4 weeks) rise in metabolic rate and drop in blood cholesterol, the diagnosis of myxedema should be

made with reservations or not at all. The solution of the problem of hypercholesterolemia and why it occurs in certain diseases is still baffling, but to find it in an individual without any physical abnormality is even more of a conundrum.

The significance of hypercholesterolemia as an aid in the diagnosis of myxedema is further enhanced by the response to desiccated thyroid. Rarely does a patient with undoubted myxedema require more than 2 grains of U.S.P. thyroid. If a blood cholesterol value cannot be lowered by at least 40% of the original value on this dose, the probability of its elevation being due to thyroid deficiency is considerable lessened. The striking reduction of hypercholesterolemia in myxedema by administration of desiccated thyroid in such doses is characteristic.

If we strike out the postoperative cases in this series, 233 cases remain which probably represent the approximate distribution among general medical cases which might be suspected of having hypercholesterolemia. Of these, 93 patients, or 40%, had spontaneous myxedema.

SUMMARY

In a group of 404 patients showing hypercholesterolemia, 65% had thyroid deficiency.

Of 233 cases of hypercholesterolemia without previous operations on the thyroid gland, 40% had spontaneous myxedema.

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THE MODERN TREATMENT OF PARATHYROID INSUFFICIENCY[1]

DIHYDROTACHYSTEROL

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IN 1926–27, Windaus and his coworkers (Chemical Laboratory of the University of Göttingen) first produced products of high antirachitic potency through irradiation of ergosterol with ultraviolet rays (1). A short time thereafter, a thousand-fold overdose of irradiated ergosterol, calculated on its antirachitic potency, was found to produce a toxic effect: loss of appetite and weight, hypercalcemia, deposition of calcium in the soft tissues (especially in the kidneys and blood-vessel walls), circulatory impairment, and gastrointestinal bleeding (2). The ergosterol derivatives prepared by various forms of irradiation were not absolutely identical. Dry preparations kept sealed in a glass tube under vacuum for a long period of time lost their antirachitic potency without losing their toxicity. The destruction of vitamin D in irradiated ergosterol by aging could also be accomplished by means of heating. Finally, if the double bonds in the irradiated ergosterol were eliminated by hydrogenation, the antirachitic potency was destroyed, while all of the toxic effect was retained (3). This proved that the toxic action of overdosage of irradiated ergosterol was not a hypervitaminosis. As the toxic principle in these preparations influenced chiefly the calcium metabolism it was called the 'Kalcinosefaktor.'

The effect of the Kalcinosefaktor resembles that of repeated injections of calcium or parathyroid extract (4). This finding raised the question whether or not the action of the Kalcinosefaktor on calcium metabolism could be utilized wherever the injection of parathyroid extract or calcium produces a more or less fleeting therapeutic effect. Such therapeutic tests seemed justified, because the Kalcinosefaktor is effective when given by mouth, and because the effect of a single dose may extend over many days and even weeks.

Pharmacologic tests were made with a large variety of animals, from the monkey to the canary (5). Parathyroidectomized dogs could be successfully treated with the Kalcinosefaktor, and thus protected from tetany (4, 6). The Windaus school thus succeeded in obtaining from crude irradiated ergosterol some pure chemical substances, and selected from these the one having the purest and most uniform calcium effect namely, dihydrotachysterol.

Moreover, after the sensitiveness of human beings to the Kalcinosefaktor had been tested in personal experiments (7), therapeutic tests were made in human beings having postoperative tetany. In the meantime, I had left the Chemical Institute at Göttingen and became associated with the Charité Hospital in Berlin, where numerous patients with tetany were to be found on the wards. First each severe case of tetany was treated with the Kalcinosefaktor until all tetanic manifestations had disappeared (6); then treatment was discontinued. One patient with postoperative tetany, whose manifest symptoms had been eliminated through treatment with Kalcinosefaktor and who appeared to be completely well, suddenly died with spastic ileus. On the day before death the patient suffered severe tetanic attacks. Furthermore, ophthalmologists have shown that a tetanic opacity of the lens may also develop without subjective disease symptoms. Other patients with latent tetany suffered acute dyspnea due to spasms of the larynx and the diaphragm. We lost test animals in the latent stage of the disease through systolic heart failure.

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[1] As a collaborator of Professor Holtz, who, as is well known, introduced the treatment of tetany with dihydrotachysterol, I have often been asked questions that I did not feel competent to answer. This paper was expressly therefore written by Professor Holtz in 1937 to answer questions concerning the applications of dihydrotachysterol and to clear up some errors as to its danger, which was over-estimated in the beginning.

The present knowledge of dihydrotachysterol is the result of systematic clinical and experimental investigation. The drug is an excellent therapeutic agent for parathyroid insufficiency. It is also of importance for research as it enables one to regulate the calcium level of the blood.

Although calcium metabolism is of paramount importance in the pathogenesis of tetany, it is neither the key to nor the direct cause of all of its forms, e.g., not for tetany of forced respiration and the tetany of gastrointestinal disorders. Moreover, while one can observe that the excitability of nerves may change instantly during injection of calcium in a case of tetany, clinically the calcium level of the blood and the excitability do not change simultaneously. If the calcium level and the excitability of nerves are graphically plotted, the curves will be similar but not synchronous. Furthermore, the appearance of symptoms and a low calcium level are not absolutely linked together. All these facts point to an indirect relationship—the involvement of more than one factor.—F. A. QUADFASEL, M.D., Department of Neurology, Bellevue Hospital, New York City.

These serious events forced us to change our method of therapy. Today we believe that each case of tetany should be treated systematically until the parathyroid glands have wholly resumed their function. In many cases, therefore, treatment will have to be continued for life (8).

In 1933 the Kalcinosefaktor was introduced commercially under the designation "A.T. 10" (Antitetanic Preparation No. 10) (9).[2] Since then the therapy of tetany with dihydrotachysterol has spread rapidly and today many practicing physicians all over the world are treating ambulant patients (10).

Knowledge of parathyroid insufficiency has grown and at present we know many forms of this disease which heretofore could never be correctly diagnosed and for which, therefore, there was no causal treatment. Parathyroid insufficiency is by no means a rare disease, but it is infrequently recognized by the physician. One does not overlook diabetes until the patient has an odor of acetone or lies in diabetic coma! Similarly, the diagnosis of parathyroid insufficiency must not be postponed until the appearance of the classic symptoms of tetany: paresthesias and spasms. If a physician knows the symptoms of parathyroid insufficiency and thinks of the possibility of this disease, he can quite frequently make the diagnosis.

CHEMISTRY AND PHARMACOLOGY

Dihydrotachysterol is available in a concentration of 0.5% in oil. In the ultraviolet irradiation of ergosterol the following substances are produced in progressive stages: lumisterol, tachysterol, vitamin D, toxisterol and suprasterol. The base of all of these compounds is the four-ring system of cyclo-pentanephenanthrene, which is found also in bile acids, cholesterol, bufagin, digitalis substances, saponin, sex hormones and in a few highly carcinogenic compounds (11). The ultraviolet irradiation of ergosterol results in a molecular rearrangement. In the transition of lumisterol to tachysterol, one of the four rings is split and a new double bond is formed. The split ring is closed again when suprasterol is formed. Thus ergosterol, lumisterol and suprasterol have four rings and three double bonds; these substances are all ineffective pharmacologically. The remaining transition products contain three rings and four double bonds, and unfold the effect of the Kalcinosefaktor. Only the vitamin D has antirachitic action and thereby regulates the phosphorus metabolism; but it also contains the Kalcinosefaktor and thereby influences the calcium metabolism (the same as tachysterol and toxisterol). The pharmacologic effectiveness grows with increasing conversion; determined in the mouse, the minimal toxic dose (M.T.D.) (12) is 0.2 mg. for tachysterol; 0.065 mg. for vitamin D, and 0.025 mg. for toxisterol. It has been reported that vitamin D and toxisterol can seriously damage the circulatory system, or lead to poisoning due to an unpredictable accumulation of these substances. Tachysterol does not have this cumulative effect, nor is its action on calcium metabolism accompanied by any undesirable by-effects. However, a solution of tachysterol is not stable. Through treatment of tachysterol with nascent hydrogen, the dihydrotachysterol is produced. This is permanently stable in oily solution and has the favorable pharmacologic effects of tachysterol.

If a human being or animal is given dihydrotachysterol by mouth, the calcium content of the blood serum begins to rise after about 48 hours, reaches its maximum after 4 to 5 days, and sinks back to normal within the course of the next few weeks. Intravenous administration of dihydrotachysterol has no advantage since the effects do not appear any more rapidly. Intramuscularly or subcutaneously it is practically without effect as this drug is apparently absorbed with great difficulty from such depots.

The serum calcium level of human beings is normally from 9.5 to 11 mg.%. In tetany, also in sprue and contracted kidney, one finds values as low as 4 mg.%. In tumors of the parathyroid glands (ostitis fibrosa generalisata, Recklinghausen), frequently also in extensive destructive processes of the skeletal system (large bone fractures, bone sarcomas and myelomas), and in polycythemia the calcium content of the serum is increased. The serum calcium, obtained by centrifuging coagulated blood, does not differ from the calcium content of paraffin or hirudin plasma. The red blood corpuscles are impermeable to calcium ions. Their calcium content fluctuates between 1 and 4 mg.%. When blood is strongly hemolyzed, the serum is diluted by the calcium-poor fluid from the erythrocytes, and the calcium concentration is low in the hemolyzed serum.

Through ultrafiltration or dialysis, the calcium of the serum can be divided into two fractions: the undialysable calcium bound to albumin ('colloidal' calcium) and the diffusible calcium. The colloidal portion constitutes about 40 to 60% of the total calcium; this proportion is often greatly decreased in tetany (to below 30%), and increased in hypercalcemia through dihydrotachysterol (up to 80%). The albumin-calcium compound in the serum develops with extraordinary rapidity; when calcium solution is injected intravenously it forms immediately. Its formation depends, among other factors, on the total calcium content of the serum, on the albumin concentration and upon such factors as the carbon dioxide content. The diffusible calcium consists of ionized

[2] In the United States dihydrotachysterol, "A.T. 10," is marketed by the Winthrop Chemical Company, Inc., New York.

calcium and undissociated calcium-containing molecules. Apparently no clinical significance attaches to these two fractions. Their separation may be accomplished through not wholly reliable electric methods.

Calcium elimination through the kidneys is, to a great extent, independent of the calcium intake through food; the calcium content of the urine parallels the calcium content of the serum and is, therefore, very low in hypocalcemia (tetany). The daily elimination of calcium in the urine of an adult is about 0.3 to 0.8 gm. If there is hypercalcemia (e.g. through overdosage of dihydrotachysterol), reversible metastatic calcium deposits develop in the kidney as well as calcium cylinders in the tubules.

Calcium elimination in the feces is reduced during treatment with dihydrotachysterol. If the food is rich in calcium the reduction of calcium in the feces exceeds the increase of urinary calcium, and the calcium balance becomes positive. Lack of calcium in the food and continued large doses of dihydrotachysterol lead to demineralization of the skeleton in the sense of an osteoporosis, without symptoms of ostitis fibrosa. Under the influence of dihydrotachysterol treatment calcium has the tendency to leave the intestine, or possibly the calcium depot in the bone, and to enter the soft tissues by means of the blood serum.

Rachitis and spasmophilia. These are disorders of the phosphate metabolism and can be cured with vitamin D. These diseases cannot be influenced through dihydrotachysterol (13), because it does not affect the phosphate metabolism, the phosphate balance or the phosphate content of the blood, so long as the phosphate metabolism is not influenced secondarily by considerable disturbance of the calcium metabolism or by renal injury.

Dihydrotachysterol can replace the parathyroid hormone in tetany, although parathyroid hormone and dihydrotachysterol are two chemically different substances which differ also in pharmacologic action. A comparison of their actions may clarify this (table 1). Various species of animals differ relatively in their sensitivity to dihydrotachysterol and parathyroid extract (4).

TABLE 1

	Dihydrotachysterol	Parathyroid hormone	Calcium salts
Clinical Effect			
Perorally	Very good	No effect	Negligible
Subcutaneously and intramuscularly	No effect	Very good	Good
Intravenously[1]	Same as by mouth	Good	Very good
Effect on Serum Calcium Level			
Onset of effect	After about 48 hours	Immediately	Immediately
Maximum hypercalcemia	After several days	After 16 to 18 hours	Intravenously, immediate; intramuscularly, within 1 hour.
End Effects			
End of action	After 1 to 3 weeks	After 1 to 2 days	After several hours
Metastatic renal calcification:	Calcification of renal tubule cells	Calcification of basal membrane of renal tubules	Calcification of basal membrane of renal tubules
Lessening of therapeutic effect through habituation:	Not observed	Observed in a few patients (14)	Marked habituation

[1] Subject to dangers of oil injection.

THERAPY

Dihydrotachysterol is administered by mouth. It may be taken on an empty stomach or after meals; the exactly measured dose may also be mixed into the food. The result of dihydrotachysterol therapy depends upon the correct dosage. Insufficient doses of dihydrotachysterol fail to overcome the clinical manifestations, while excessive amounts may cause such toxic symptoms as loss of appetite, nausea and vomiting. Overdosage can be determined with certainty only through determination of the blood calcium level.

The individual requirements of dihydrotachysterol vary greatly, so that the needed dose for each patient must first be carefully determined. Even in the same person the required dose of dihydrotachysterol varies with increased physical labor or mental exertion and in pregnancy. Dihydrotachysterol therapy must be carefully guided and watched by the physician.

Treatment with dihydrotachysterol must not be interrupted when another disease develops (e.g. nephritis, tuberculosis, etc.); experience has taught that especially large doses of dihydrotachysterol are frequently required at such times.

Dosage. Guides for determining the dose of dihydrotachysterol are the condition of the patient and the height of the serum calcium level, which should, if possible, be kept between 9.5 and 11.0 mg.%. If the clinical symptoms are mild, it is best to begin treatment gradually with small amounts: 5, 10 or 30 drops[3] of dihydrotachysterol daily, or 1 to 6 cc. once a week, depending on the serum calcium level. With serum calcium below 6 mg.%, 30 drops daily or 6 cc. weekly may be given; with serum calcium above 9 mg.%, 5 drops daily or 1 cc. weekly. Accurate serum calcium analyses should be made every 2 or 3 weeks.

If symptoms of manifest tetany with marked hypocalcemia are present, large doses of dihydrotachysterl are given from the start: 8 to 15 cc. in a single dose, followed by a daily dose of 1 cc. The blood

[3] 1 cc. equals from 30 to 35 drops.

calcium is checked on about the seventh day of treatment.

In an acute attack of tetany, it is best to inject calcium intravenously, after previous withdrawal of blood. Calcium gluconate is preferred, because it may also be injected intramuscularly and because it does not cause abscess formation in case of paravenous injection. As soon as the acute tetanic attack has subsided, dihydrotachysterol is administered.

Up to 15 cc. of dihydrotachysterol may be given without serum calcium determination, either in large individual doses (e.g. 5 cc. 3 times within 2 days) or in divided doses (e.g. 5 drops twice daily). Before additional doses of dihydrotachysterol are given, the serum calcium level should be checked. Severe cases of manifest tetany which need daily injections of calcium may be given 20 cc. of dihydrotachysterol without previous blood examination. Under certain conditions, if the tetanic symptoms are of grave nature, it is advisable to give up to 60 cc. of dihydrotachysterol over a 3-day period. Before giving additional doses of dihydrotachysterol, the serum calcium level should be checked. In checking the serum calcium level it should be noted that the effect of a large dose of dihydrotachysterol on the blood calcium content is demonstrable at the earliest after 2 or 3 days, and that the maximal effect is reached between the 4th to 7th day.

The fluctuations of the serum calcium level during the first period of treatment serve as a basis for fixing the subsequent dosage. The more closely the calcium level approximates the normal, the smaller should be the doses that are given. Sometimes the serum calcium level drops at the beginning and the tetanic symptoms disappear; in such cases also the dosage must be considerably reduced. If the calcium level remains constant (e.g. 9.6 mg.%) despite the administration of dihydrotachysterol, the dosage should be gradually increased. Blood calcium analyses are repeated at intervals of from 2 to 4 weeks until the dosage has been determined which constantly maintains the calcium level between 9.5 and 11.0 mg.%, which is optimal for the well-being of the patient. Patients should be told of the dangers connected with the interruption or careless execution of dihydrotachysterol therapy. They should report to the physician every 2 or 3 months for a check of the serum calcium level and of the general condition. Each substantial increase in dihydrotachysterol dosage must be followed by repeated calcium controls at intervals of about 2, 4, or 6 weeks.

In rare instances the first doses of dihydrotachysterol may cause an exacerbation of the condition. The patient may complain temporarily of cardiac palpitation, weakness, mild nausea and headache. However, these symptoms always disappear within a short time, even without interruption of dihydrotachysterol therapy. In highly sensitive persons this stage can be readily overcome through beginning with minimal doses (1 drop daily) and increasing the dosage slowly. Most patients with parathyroid insufficiency continuously need from 10 to 30 drops of dihydrotachysterol daily, or from 2 to 6 cc. weekly. In cases of hemorrhage (22) or chronic pain due to varicosities (23), from 3 to 10 cc. of dihydrotachysterol should be given in a single dose once or twice.

Dihydrotachysterol is compatible with all other medicaments. Its action is enhanced by the addition of thyroidin or acidifying salts (through mobilization of the bone calcium) and also, to a slight degree, by the addition of calcium. It is advisable, however, to abstain from such supplemental therapy, if at all possible. In difficult cases, combination therapy with parathyroid extract is recommended, as the action of the two agents is synergistic.

Occasional patients were found to be hyposensitive to dihydrotachysterol. Even with massive doses it is sometimes impossible or difficult to raise the calcium level and to eliminate the clinical symptoms. With some of these patients the cause is poor absorption of the dihydrotachysterol from the intestinal tract; depancreatized dogs react to the peroral administration of dihydrotachysterol only when desiccated or fresh pancreas is given simultaneously. If pancreas tablets are prescribed together with dihydrotachysterol, it is advisable to have the patient chew the tablets in the mouth, for otherwise they will remain in the stomach for a long time and thus will not reach the intestine simultaneously with the dihydrotachysterol.

A patient's dihydrotachysterol requirements are independent of the original severity of the clinical picture.

Dangers of dihydrotachysterol therapy. Originally, when experience with dihydrotachysterol was limited, we continually warned against dangers. Today we know that the dangers were overestimated.

A rapidly transient hypercalcemia (up to or above 15 mg.%) following overdosage of dihydrotachysterol is tolerated without bad after-effects. However, it is important that such overdosage should be recognized in time, so that it does not persist for weeks, a circumstance which will lead to severe damage. In most cases, reduction of the dose or interruption of dihydrotachysterol therapy suffices to eliminate promptly the hypercalcemia. Intramuscular injection of large doses of follicular hormone (about 100,000 I.U.) will hasten reduction of the serum calcium level. In some conditions (such as a number of vascular disturbances) a temporary hypercalcemia is even desirable from a therapeutic standpoint.

The first symptoms of dihydrotachysterol overdosage are loss of appetite and nausea; next follow thirst and exhaustion, frequently also constipation. Often, however, the patient does not notice the hypercalcemia.

Once the serum calcium of a patient with parathyroid insufficiency has been adjusted to a normal level through regular administration of dihydrotachysterol, the level does not rise suddenly. It is sufficient, therefore, to make control analyses every 2 to 4 months. However, varying external influences (such as febrile diseases, pregnancy and physical exertion) may demand an increase in the amount of dihydrotachysterol; with a fixed dosage of dihydrotachysterol these influences may lower the calcium level and lead to recurrent paresthesias. If, for instance, a sedentary worker with tetany engages in active sport during his vacation, the dosage of dihydrotachysterol must be considerably increased during that period.

Pregnancy, sex glands and dihydrotachysterol requirements (24). During the course of pregnancy, every case of tetany tends to change into a severe, manifest form, thus endangering the life of mother and child. Women with a relative parathyroid insufficiency may usually appear completely well, but during the second half of pregnancy they may present manifold symptoms of parathyroid insufficiency, so that temporary dihydrotachysterol therapy is indicated.

Numerous tests on parathyroidectomized female dogs have taught us how pregnancy can be safely brought to full term despite existing tetany. At a certain time of pregnancy the dihydrotachysterol requirements are suddenly increased, not declining to the original norm until after parturition. In human pregnancy this time comes at about the end of the fourth to fifth month. Simultaneously the fetus starts to gain weight and continues to grow at a constant rate until birth. Furthermore, calcium begins to be deposited in the skeletal parts of the fetus. In a pregnant woman with tetany, receiving dihydrotachysterol treatment, blood calcium determinations must, therefore, be made every 2 to 3 weeks, beginning during the fourth month of pregnancy. As soon as the calcium level falls, the dosage of dihydrotachysterol should be doubled or trebled; frequently, additional increases must be made during the succeeding months. With the onset of labor all dihydrotachysterol treatment should be stopped.

In parathyroidectomized dogs with a calcium level previously adjusted to normal with dihydrotachysterol, the serum calcium level can be lowered to the point of tetany through the injection of follicular hormone, despite constant treatment with dihydrotachysterol. In normal, perfectly healthy dogs also very high doses of follicular hormone can produce a decrease in the blood calcium level and sometimes tetany. Thus follicular hormone has an antagonistic action upon parathyroid hormone and dihydrotachysterol, a fact which can be utilized in case of dihydrotachysterol overdosage. However, it is known that large doses of follicular hormone administered to dogs produce an often fatal thrombopenic purpura (25); to what extent follicular hormone is able to increase hemorrhagic tendencies in man, is uncertain. At any rate, these observations necessitate caution. Perhaps there is some connection between these facts and the observation that single, large doses of dihydrotachysterol may arrest hemophilic as well as thrombopenic hemorrhages (22).

The antagonism between follicular hormone and the parathyroids may be the cause for the prevalence of tetany in women: over 80% of our patients with parathyroid insufficiency belong to the female sex. The male sex hormone and the corpus luteum hormone apparently have no influence upon the body's requirements of parathyroid hormone.

Our experiences with dihydrotachysterol now extend over more than 6 years. So far no case has been observed wherein a patient has been injured through dihydrotachysterol therapy, although some tetany patients have taken the preparation for 6 years, and although dihydrotachysterol has been given to ambulant patients by a large number of physicians far from clinics, for a number of years. However, everyone who prescribes dihydrotachysterol must realize that unwise prescription of the medication and lack of control of the patient may result in as much serious harm with dihydrotachysterol as with other medications.

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Abstracts of
CURRENT CLINICAL LITERATURE

Editor: HANS O. HATERIUS. *Collaborators:* E. B. ASTWOOD, ISRAEL BRAM, JOHN C. BURCH, JOHN C. DONALDSON, MURRAY B. GORDON, ARTHUR GROLLMAN, E. C. HAMBLEN, FRANK A. HARTMAN, R. G. HOSKINS, J. E. HOWARD, ALLAN T. KENYON, J. T. LEWIS, JOSEPH M. LOONEY, A. E. MEYER, C. C. PFEIFFER, GEORGE W. THORN, EMMERICH VON HAAM.

THYROID

BRØCHNER-MORTENSEN, K., AND E. MØLLER.

On creatinine in thyrotoxicosis. *Acta med. Scandinav.* 102: 417. 1939.

In 51 patients with thyrotoxicosis no relationship was found between the B.M.R. and the amounts of creatine and creatinine in the urine. Increased creatine excretion (200 mg./24 hr.) was found in 25 patients before I treatment, and a decreased excretion after I treatment in 9 patients. During and after x-ray treatment of 13 patients and after subtotal thyroidectomy there was no change in creatinuria. It is concluded the estimation of urinary creatine and creatinine is of no value in the clinical examination of thyrotoxic patients.—J. F. Wilkinson.

BRØCHNER-MORTENSEN, K., AND E. MØLLER.

On the cholesterol content of the blood serum in thyrotoxicosis. *Acta med. Scandinav.* 103: 259. 1940.

In 51 patients with thyrotoxicosis the total serum cholesterol generally lay within the limits found in normal persons. Before treatment was started the average value was 184 mg. %, rather lower than that of normal persons. In the material as a whole no correlation was found between serum cholesterol and B.M.R. In the repeated examination of 49 patients it was found that in 32 (65%) the changes in serum cholesterol tended to be inversely proportional to the changes in B.M.R. In the examination of 7 patients after thyroidectomy the serum cholesterol showed a marked rise —J. F. Wilkinson.

BRUCH, F.

Obesity in childhood—II. Basal metabolism and serum cholesterol of obese children. *Am. J. Dis. Child.* 58: 1001. 1939.

Determinations of B.M.R. for 72 obese children and serum cholesterol determinations for 89 are reported. The total B.M.R. of obese children was higher than that of normal children of comparable height and age. The mean value of total serum cholesterol is 200.3 mg. per 100 cc. and the relation of combined to free cholesterol is 2.60± 0.24. No relation between the serum cholesterol concentration and the basal rate was revealed in this study. Thyroid medication had no influence on the weight or serum cholesterol concentration.—*M.B.G.*

BRUNNER, R., AND L. LEED.

Blood pressure and pulse rate changes during thyroidectomy. *Surg., Gynec. & Obst.* 70: 731. 1940.

Blood pressure and pulse readings were analyzed in over 600 patients with varying degrees of thyrotoxicosis. A direct relationship was established between the rise in blood pressure and the degree of toxicity at time of operation. The pulse rate furnished the best index as to prognosis.—L. B. Shpiner.

CRAWFORD, T.

Carbohydrate tolerance in hypothyroidism and hyperthyroidism. *Arch. Dis. Childhood* 15: 184. 1940.

In conditions of hypothyroidism carbohydrate tolerance is impaired. This impairment is due to a general slowing of the processes of katabolism and possibly also to a diminution in rate of storage of carbohydrate. The low oral blood-sugar curve which occurs frequently and which accounts for the textbook statements that carbohydrate tolerance is increased in hypothyroidism, is due to slow absorption of the carbohydrate from the bowel. In hyperthyroidism also there is impairment in tolerance, the fault being traceable to defective glycogen formation. This probably results from the excessive secretion of thyroxin causing an increased liberation of adrenalin, which in its turn mobilizes hepatic glycogen and inhibits its re-formation. Ten case histories are summarized.—Author's summary.

CUTLER, E. C., AND S. O. HOERR.

Total thyroidectomy for heart disease. A five-year follow-up study. *Ann. Surg.* 113: 245. 1941.

A 5-year follow-up study was made of 57 cases in which total thyroidectomy was performed for heart disease. These included 32 of angina pectoris and 25 of congestive heart failure, with 12 survivors in the former group, 4 in the latter. There were 5 postoperative deaths; 4 of these and all but 3 of the later deaths were attributable to heart disease. The best results were obtained in patients with angina pectoris. Eight of the 12 survivors in this group had sustained relief from pain and all but one of 27 patients who survived for 6 months or longer were relieved to some extent. It was noted that preoperative evidence of congestive failure or cardiac enlargement in patients with angina pectoris was an unfavorable prognostic sign for

long survival. In the patients with congestive failure the results were disappointing. Three of the 4 survivors in this group experienced sustained relief, 15 of 25 who lived for 6 months or longer had relief for 6 months or longer. Results were better in patients with congestive failure due to chronic rheumatic valvular disease than in those with arteriosclerotic or hypertensive heart disease. No serious difficulties were encountered in the control of postoperative myxedema. It was concluded that in a selected group of patients with intractable angina pectoris, total thyroidectomy is a worth-while therapeutic measure and is without unwarranted risk.—*J.C.B.*

GREENE, A. M.

Iodine and cholesterol metabolisms in patients with primary myxedema. A clinical and experimental study with a report of results of treatment. *Arch. Int. Med.* 67: 114. 1941.

The cholesterol level of the blood was elevated in 9 cases of thyroid deficiency studied. After treatment with thyroid preparations was begun the level fell in reciprocal relation to the rise of B.M.R. The level proved a good criterion of amount of thyroid substance needed after beginning of treatment. In a case of compensated myxedema without hypometabolism, thyroxin administered intravenously and dessicated thyroid given orally exerted no effect on level of blood cholesterol. The specificity of I present only in thyroid preparations in lowering the level was demonstrated in 1 case of myxedema; inorganic I (Lugol's solution) failed to alter the blood level, both findings corroborating those found elsewhere. As for I metabolism, giving dessicated thyroid to a myxedematous patient produced an I diuresis analogous to that seen in spontaneous hyperthyroidism. No absolute correlation could be observed between variations in level of I and that of cholesterol in myxedema, but there was a tendency for the level of organic I to vary inversely with that of plasma cholesterol. The study demonstrated the need for more extensive studies of I metabolism in myxedema with longer periods of study of hospitalized patients and more knowledge of the I ingested in food and excreted in feces.—*W. C. Hunter.*

JONES, R. M.

Human sternal bone marrow in hyperthyroid and myxedematous states. *Am. J. M. Sc.* 200: 211. 1940.

Sternal marrow aspirated from 18 "normal" individuals contained an average of 6.2% nucelated cells. Sternal marrow from 12 individuals with hyperthyroidism contained an average of 13.5% nucleated cells, about 2 1/5 (217%) times the "normal" finding. Sternal marrow from 7 individuals with hypothyroidism contained an average of 2.4% nucleated cells, a little more than one-third (38%) of the "normal" average. Five cases of hypothyroidism treated with desiccated thyroid or thyroxin, and subsequently studied, showed a marked rise in the percentage of nucleated cells in the sternal marrow. A case of thyrotoxicosis following thyroid ingestion showed a marked decrease in the percentage of nucleated cells in the marrow when the thyroid was stopped. There was a less marked but definite decrease in cases where subtotal thyroidectomy was performed. The hyperplasia found in the marrow of the hyperthyroid individuals was myeloid in character, and was not reflected in the peripheral blood. —Author's abstract.

KENNEDY, R. L. J.

Surgical and medical treatment of exophthalmic goiter of children. *Am. J. Dis. Child.* 60: 676. 1940.

Follow-up studies were made of 171 patients seen at the Mayo clinic during childhood because of exophthalmic goiter. Of 163 who sent in reports, 138 had been treated surgically and 25 medically. The ratio of ♀ ♀ to ♂ ♂ was 7.5 to 1. The ages ranged from 3 to 14 years. Good results were obtained in 32.4% of patients operated upon before the introduction of I and in 67.5% after I came into use. The surgical mortality rate before the use of I was 9% and only 3.3% after iodine was introduced. Later deaths from thyroid disease, recurrences and the necessity for subsequent operations were less frequent among patients operated upon after the introduction of iodine. Low metabolic rates and postoperative myxedema were more frequent in the group in which treatment consisted of extensive resection rather than ligation of vessels or ligation and partial resection. Medical treatment was carried out in 25 patients but 7 had to be operated upon subsequently. Children with exophthalmic goiter apparently grew more rapidly than so-called normal children but their ultimate height was neither greater nor less than the average height.—*M.B.G.*

LERMAN, J.

Iodine components of the blood. Circulating thyroglobulin in normal persons and in persons with thyroid disease. *J. Clin. Investigation* 19: 555. 1940.

Rabbits injected with human thyroglobulin by various routes produced antibodies in high concentration. In precipitin reactions such antiserum could detect minute amounts of thyroglobulin in solution, e.g., 0.08 to 0.15 mg. per 100 cc., or ¼ to ½ γ % of thyroglobulin I. No detectable amounts of thyroglobulin were discovered in the blood of numerous normal, 2 myxedematous, 15 thyrotoxic patients before iodinization, nor in 2 thyrotoxic subjects after iodinization. Similarly, no thyroglobulin was detected in the urine of 3 hyperthyroid subjects. The excess I usually present in the blood of hyperthyroid patients is evidently not due to circulating thyroglobulin. Blood obtained directly from the thyroid veins at operation was similarly tested. Ten of 12 samples obtained at beginning of operation were negative; 2 samples obtained at the end of hemithyroidectomy (unoperated side) were also negative. Seven of 8 thyroid vein samples obtained during or at the end of the 2nd stage of subtotal thyroidectomy showed appreciable amounts of thyroglobulin, 0.2 to 13.0 mg. per 100 cc. It disappeared from the circulation within 12 to 36 hours after operation. The presence of thyroglobulin in the blood is apparently due to the extrusion of colloid into the circulation by trauma, and thyroglobulin does not ordinarily leave the follicles as such. This deduction is consistent with observations of Williams on the release of colloid from living thyroid follicles.—Author's abstract.